Living with a genetic form of arrhythmogenic right ventricular cardiomyopathy causing sudden cardiac death: Symptoms of depression, anxiety and post-traumatic stress in transmembrane protein 43 p.S358L mutation positive family members with an ICD

by

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ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) caused by a p.S358L mutation in *TMEM43* has a high incidence in Newfoundland and Labrador (NL), with sudden cardiac death (SCD) often the first symptom. Implantable cardioverter defibrillators (ICDs) are effective at preventing SCD. Mental health effects have not been studied in this population. This study sought to identify symptoms of depression, anxiety, and posttraumatic stress in those with *TMEM43* p.S358L ARVC and an ICD.

TMEM43 p.S358L positive individuals with an ICD were recruited. Participants completed the Patient Health Questionnaire-9 (PHQ-9), Zung self-rating anxiety scale (SAS), and the posttraumatic checklist-civilian version (PCL-C). Prevalences of depression, anxiety and posttraumatic stress symptoms were described and compared with scores in unaffected family members and general population norms.

Fifty-three ICD patients completed the questionnaires. Univariate linear analysis revealed that the three scales were significantly positively related to each other (Pearson's $r > 0.6$). Anxiety was related to number of appropriate ICD discharges ($B=0.355$, $p=0.022$) and the PCL-C scale was significantly related to age ($B=-.322$, $p=0.019$). Multivariate regression models predicting each scale score revealed that only the three scales contributed to the variance, excepting age, which remained significant in the model predicting posttraumatic stress scale scores ($B=-.215$, $p=0.015$). A significant percentage of participants scored above the clinical cutoff levels for

depression (28.3%), anxiety (49%) and posttraumatic stress (32%). Scoring high on one mental health scale (PHQ-9, SAS, or PCL-C) was strongly associated with scoring high on the subsequent scales. Findings can inform the provision of mental health services to these patients.

GENERAL SUMMARY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart condition which often causes sudden cardiac death (SCD) in young people. In Newfoundland and Labrador (NL), one genetic variant (p.S358L in *TMEM43*) causes disease in many families. Treatment with an implantable cardioverter defibrillator (ICD) prevents SCD in this population: mental health effects have not been addressed. We sought to measure levels of depression, anxiety, and posttraumatic stress levels using three short screening scales (the PHQ-9, SAS, and PCL-C). We assessed whether severity of illness affected the scores. We also compared scores to those from spouses and unaffected siblings, and to general population norms.

A significant proportion of the 53 ICD participants scored high on the scales, revealing a prevalence of 28.3%, 49%, and 32% in depression, anxiety, and posttraumatic stress symptoms, respectively. Scores were higher when compared to the general population, and to mutation negative siblings and unaffected spouses, with the exception of posttraumatic stress prevalence highest in unaffected spouses. Each of the scale scores and age had the largest effect on the scores.

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I would like to extend my sincerest gratitude to all those who contributed to this work and to those who have provided support and guidance to me over the past few years.

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This is a 3-part project, involving 3 M.Sc. students working on different aspects of the project. While I covered the ICD patients, my fellow student colleagues focused on the other aspects of the project and provided valuable insights and information throughout the process, culminating into this final project. I would like to acknowledge Mary Walsh and Natalie Butt for their ongoing guidance, information, and insights, as well as their practical assistance in the data collection process, which was so crucial to the completion of the project.

I would also like to acknowledge prior publication of a figure included in my thesis, Figure 2.1 on page 16. This was an open source document with permission of figure use granted through the creative commons (CC) license to the journal. I would also like to thank Dr. Hodgkinson for intellectual property that she gave permission to use in this thesis, Figure 3.1 on page 54 in regards to an updated pedigree of ARVC families. Applicable copyright material forms have been submitted.

CO-AUTHORSHIP STATEMENT

I am the sole author of all parts of my thesis. The other team members contributed with ideas and discussion, in addition to data contribution from their own respective projects, that was used to compare results among the 3 groups. However, data analysis and results were all individually completed by each MSc candidate. The pedigree figure was contributed from Dr. Hodgkinson (as discussed above).

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ABBREVIATIONS AND SYMBOLS

ACS	Acute Coronary Syndrome
ANOVA	Analysis of Variance
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
ARVD5	Arrhythmogenic Right Ventricular Dysplasia
CHANNAL	Consumers' Health Awareness Network of NL-Mental health support line
CMR	Criteria for Magnetic Resonance
DNA	Deoxyribonucleic acid
DSM5	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
GAD	Generalized Anxiety Disorder
HADS	Hospital Anxiety and Depression Scale
HAM-A	Hamilton Anxiety Rating scale
HAM-D	Hamilton Depression Rating scale
HREB	Health Research Ethics Board
ICD	Implantable Cardioverter Defibrillator
IES-R	Impact of Events scale-revised
LVE	Left Ventricular enlargement
MDE/MDD	Major Depressive episode/Major Depressive Disorder
MSPSS	Multidimensional Scale of Perceived Social Support
NL	Newfoundland and Labrador

PCL-C	Post traumatic checklist- civilian version
PHQ-9	Patient Health Questionnaire-9
PRWP	Poor R wave Progression
PTSD	Posttraumatic Stress Disorder
QOL	Quality of Life
RV	Right ventricle
RVEDVI	Right ventricular Ejection dysfunction
RVEF	Right ventricular ejection fraction
SAS	Zung Anxiety scale
SCD	Sudden cardiac death
TFC	Task Force criteria
TMEM43	Transmembrane Protein 43
VIF	Ventriculoinfundibular fold
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

APPENDICES

CHAPTER 1: INTRODUCTION

Overview

Inherited cardiomyopathies are a major cause of heart disease in all age groups, often with onset in adolescence and early adult life. Despite considerable heterogeneity, they are classified according to functional and morphological features; these diagnostic classifications are helpful for evaluating complications and treatment options. One category of inherited cardiomyopathies are the Arrhythmogenic Right Ventricular Cardiomyopathies (ARVC) (Watkins, Ashrafian, & Redwood, 2011).

ARVC is a genetic disorder caused by 16 currently known genes, with several genes remaining to be discovered. This is usually an autosomal dominant disease that affects the desmosome. Abnormal desmosomes compromise cell-to-cell adhesions at intercalated discs in the heart, lessening the ability of myocytes to withstand mechanical forces during a cardiac cycle (pumping of the heart). Mutant desmosomes can also remodel gap junctions, which also cause electrocardiographic changes and arrhythmias (Ohno, 2016). The main feature of ARVC is a fibrofatty replacement of the myocardium, mainly in the right ventricle but also in the left ventricle. This change essentially results in the clinical feature of susceptibility to ventricular arrhythmias.

One genetic subtype of ARVC has a high incidence in Newfoundland and Labrador, caused by a founder (the families all link back to one ancestor) mutation (p.S358L) in the *Transmembrane*

protein 43 (TMEM43) gene. The *TMEM43* gene was discovered by the Memorial sudden cardiac death (SCD) team. This team has researched and clinically cared for this population since 1998 (HREB 00-176). This genetically homogenous subtype of ARVC currently affects 27 Newfoundland families, the largest of which comprises >1200 individuals over 10 generations. The natural history data for this patient population (natural history is the untreated course of a disease from birth to death) shows that 50% of males die before aged 40 years, and 80% before aged 50 years. The equivalent figures for women are 5% and 20%, respectively (Hodgkinson et al., 2013).

Treatment of inherited cardiomyopathies, and ARVC in particular, can be both pharmacological and non-pharmacological. Goals of treatment include prevention of heart remodelling, improved functional heart capacity (and associated treatment of heart failure symptoms) and prevention of ventricular arrhythmias that can lead to SCD. SCD is a tragic complication of a number of genetic heart diseases. In ARVC, and in the *TMEM43* p.S358L ARVC subtype in particular, SCD may be the first (and only) clinical symptom (Hodgkinson et al., 2005).

Historically, there was little in the way of treatment to offset early SCD. However, the introduction of implantable cardioverter defibrillator (ICD) therapy played an important role in prevention of SCD. Most patients receive an ICD late in life for issues related to ischemic cardiac disease and the complications of cardiac remodelling that may indeed lead to electrocardiographic changes and life threatening arrhythmias. In the case of inherited cardiomyopathies and ARVC in particular, the goal of treatment is largely the same, except that the treatment groups often

differ in severity of disease and age. Those with ARVC show clinical signs of non-ischemic heart disease much earlier in life and may require treatment as early as adolescence, which is a different clinical profile as compared to those with ischemic heart disease and an ICD.

The ICD is a pacemaker sized device that is placed in the upper left chest. It monitors heart rhythm. When a potentially lethal rhythm is detected, it can initially provide anti-tachycardic pacing to disrupt the tachyarrhythmia. If this does not work, it provides an electrical discharge internally to return the heart to normal rhythm. It records all heart activity at all times, so provides a record for the clinical team of the type of treatment (pacing or discharge) that has been administered. These electrical discharges can be appropriate (that is, they have changed a lethal rhythm to a normal rhythm) or inappropriate (they provide a shock for a non-lethal rhythm that would have terminated on its own) (Amiaz et al., 2016). If the patient remains conscious when the discharge occurs, the result has been described as equivalent to ‘a strong kick from a horse to the middle of the chest'. Individuals are knocked off their feet by the discharge and sometimes lose consciousness. A discharge therefore, whether appropriate or not, may be a traumatic event.

In relation to the disease process itself and treatment related to the ICD, the ARVC population is confronted with a variety of issues. Difficulties can include diagnosis acceptance and concerns related to genetic inheritance, limitations in daily activities, as well as lifelong medical surveillance and an ever-present fear of SCD. The ICD is the only effective therapy to prevent SCD in this population. While the shock delivered by the ICD may be lifesaving, fear of the

shock and other psychological consequences following a shock are important things to consider as well (Watkins et al., 2011).

In the *TMEM43* p.S358L ARVC population cohort, treatment is available with the ICD. This has been shown to alter the survival in this population up to an additional 30 years (Hodgkinson et al., 2016) and is the only effective therapy for individuals who otherwise face an early death. However, the mortality implications, the genetic risk to relatives, and the appropriate and inappropriate ICD discharges all may be considered stressors culminating in potential mental health sequelae.

The Problem

Despite increased awareness, consistent monitoring, and better physical health outcomes in this patient population, one area of research that is lacking is an assessment of the mental health of these individuals. The psychological consequence of ICD therapy in young people with genetic heart disease is poorly understood. Limited literature exists regarding the impact of the ICD in younger populations with genetic heart disease.

There is little research on the psychiatric well-being of young adults with genetic heart disease and ICDs. The focus of data has been on older individuals, and not necessarily in those with genetic forms of cardiomyopathy, often requiring ICD devices at a much younger age as compared to the general population. Several studies have examined these psychological sequelae as well as

quality of life (QOL) parameters in those with an ICD, but few have looked at ARVC diagnoses specifically. The results have been conflicting. Most of the evidence shows that overall, patients cope well with the ICD device but there are certain subsets of the group that are more vulnerable to psychological distress. Factors such as younger age of implantation, female sex, multiple shocks by the ICD device as well as longer time to first shock, and history of psychiatric disease have all been implicated in past studies as potential risk factors for further psychiatric sequelae in this population (Versteeg et al., 2017; Rahmawati et al., 2013; Thylen, Moser, Stromberg, Dekker, & Chung, 2016). The presence of depression, anxiety, and posttraumatic stress in this population correlates to poor compliance with medical or medication follow up, and increased morbidity and mortality (Rahmawati et al., 2013; van den Berk-Clark et al., 2018; Karatzias & Chouliara, 2009; Kikkenborg, Berg, Thygesen & Svendsen, 2014). Due to these factors, it is important to identify patients who may require additional psychological supports.

Limited research exists on this topic with regard to the *TMEM43* p.S358L ARVC population. Using a GELs research model (Genetics, Ethical, Legal and Social issues), a first phase of which included interviews with family members affected by ARVC (including those with ICDs, their unaffected siblings, and spouses), findings revealed serious mental health issues, and clinical observation from both the genetics and ICD clinics concurs. A recent qualitative study based on interviews with ICD recipients and their family members (mean age of participants was 46 years) provides empirical data that mental health issues occur across a range of areas including social life, recreational activities, relationships and economic burden (Etchegary et al., 2016; Etchegary

et al., 2017). We do not know how prevalent mental health outcomes are in the participants of the study that comprise the families with this type of ARVC, nor do we have any information regarding the factors that might increase or decrease those outcomes. This study provided evidence of mental health morbidity in families affected by ARVC. In conjunction with clinical observations and ongoing conversations with families, it was the catalyst for the current study – a quantitative analysis of the mental health impacts of living with this genetic subtype of ARVC.

This research project will focus on identifying mental health sequelae, namely depression, anxiety, and posttraumatic stress symptoms, in the *TMEM43* p.S358L mutation positive individuals with an ICD and assess whether their mental health states relate to the severity of their cardiac disease: their lived experience of having the disease. Secondarily, comparison will be made to the prevalence of the same mental health issues in the general population. Thirdly, comparisons will be briefly made using data from their unaffected siblings (who were born with the same genetic risk but shown to not carry the mutation) and (b) spouses of the ICD patient cohort. Given the lifelong impact of the ICD, and given the anecdotal evidence we have from our patient clinics, we feel it is vital to explore the psychological ramifications associated with having this *TMEM43* mutation and the treatment used to offset early death. We wish to obtain data that will either support (or not) the need for our clinics to provide mental health support alongside cardiac care.

We hope this data will lead to improved mental health services and psychiatric outcomes. This is

an important observational study that can provide insight into the mental health following ICD treatment in this younger cohort of patients.

RESEARCH OBJECTIVES

This research project focuses on the mental health of an ARVC cohort from the Newfoundland founder population, where the disease is caused by a p.S358L disease causing variant in a gene called *TMEM43*. The disease is a cause of SCD.

The total project comprises three groups which include (a) persons with the p.S358L mutation, who have an ICD for prevention of SCD, (b) siblings of those persons with an ICD who were born at an *a priori 50%* risk of having the p.S358L in *TMEM43* who were shown NOT to have the mutation and thus were deemed free of the disease and (c) the unaffected, non-biologically related spouses of those with an ICD. Each section of the research project sought to identify symptoms of depression, anxiety, and posttraumatic stress in each group. My particular thesis will focus on the ICD participant group.

The primary objectives are the following: to determine the prevalence of depression, anxiety, and posttraumatic stress symptoms in the ICD group, including how it compares to general population norms; and to determine whether the severity of psychiatric symptoms correlates with severity of disease in the ICD group (represented by a variety of demographic and clinical variables).

We will include comparisons of psychiatric symptom prevalences between the three groups (ICD group, mutation negative siblings group, unaffected spouses). The data obtained from the study may alter the provision and type of health care in this patient cohort regarding their mental health.

Our null hypothesis states that mutation positive ICD recipients will score higher on these scales as compared to general population prevalences, the unaffected siblings group and the biologically unrelated spouses group.

CHAPTER 2: LITERATURE REVIEW

There is scarce research available on the topic of mental health in genetic cardiac disease; there is even less on the specific condition of ARVC. A literature search using PubMed, The Cochrane Library, PsychiatryArticles and the Clinical Trials database was completed. PubMed yielded the greatest number of results. The other databases yielded no new search results as compared to PubMed results. Using the MeSH terms “psychological stress” and “implantable cardioverter defibrillator” in PubMed, yielded the greatest number of results (117), 23 of these having some relevance to our study. Other searches included MeSH terms “implantable cardioverter defibrillator” with “depression”, “anxiety”, and “posttraumatic stress” as additional separate variables. These separate searches yielded total results of 151, 190, and 31, respectively. All but one article

on posttraumatic stress overlapped from the original search results. Relevant articles related to references from used articles were also reviewed, if applicable. This yielded an additional nine references. The criteria for relevant studies included diagnostic implications rather than treatment methods, a focus on depressive, anxiety, and posttraumatic symptoms, and on younger age groups. Nonetheless, a number of studies have described psychological difficulties and mental illness in cohorts of older patients with ICDs: the more usual recipients for ICDs as the treatment of choice following myocardial infarct.

A literature search for the terms “arrhythmogenic right ventricular cardiomyopathy” and “implantable cardioverter defibrillator” yielded over 200 articles related to ICDs in general, with approximately 12 articles having some relevance to our study. Articles that related to non-ischemic forms of heart disease and to mental health (depressive, anxiety, and/or posttraumatic symptomatology) were preferentially assessed. Further MeSH term searches of ARVC and ICD, with additions of depression, anxiety and posttraumatic stress yielded one article each. There have been no studies done on the mental health of the ARVC subtype caused by the specific genetic mutation in *TMEM43* (p.S358L).

The purpose of our study was to add to the small number of studies on mental health in ARVC populations. Limited research in this area may be due to the fact that ARVC is a rare disorder. In addition, research has focused on clinical management of the high SCD risk with the disease; thus, mental health has been understudied in this population. However, it is evident from our

literature search, and our experience with a large ARVC population, that such studies require further exploration.

This literature review will comprise two major sections. Initially, we will present an overview of ARVC in terms of the biological, genetic and overall medical understanding of the disease and its current treatment approach. This includes a discussion regarding the specific genetic mutation that occurs in NL, Canada. It is important to have a solid foundational understanding of the disease itself to be able to appreciate the mental health burden that may accompany it. The second section will focus on literature that examines mental health in patients with an ICD and then specifically, those who have a device due to genetic heart disease.

Part One: An overview of arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy

ARVC/D was potentially first described historically in 1736 by Giovanni Lancisi, the Pope's physician, in his book *De Motu Cordis et Aneurysmatibus*. He reported on a family who had experienced heart failure and SCD in four generations. The first modern clinical description of the disease was reported by Marcus et al. (1982), when 24 adult cases with ventricular tachyarrhythmias with left bundle branch morphology were reported (Romero, Mejia-Lopez, Manrique, & Lucariello, 2013).

This disease was initially named arrhythmogenic right ventricular dysplasia (ARVD), but the more common term used today is arrhythmogenic right ventricular cardiomyopathy (ARVC). For the purposes of this thesis, we will use the more common ARVC terminology. ARVC is an inherited cardiomyopathy with onset ranging from adolescence to late midlife. It is characterized pathologically by myocardial atrophy, fibrofatty replacement, fibrosis and ultimate thinning of the ventricular wall with chamber dilation. This is potentially caused by abnormalities in the heart cells that connect to each other through cell-cell contacts known as the intercalated disc, with abnormalities in a portion of the intercalated disc called the desmosome. This abnormality creates a disruption in the normal structure and function of certain proteins, leading to a "pulling apart" of these cell contacts. This is not secondary to ischemia, hypertension or valvular heart disease (Towbin et al., 2019).

The estimated prevalence of ARVC in the general population ranges from 1:1000 to 1:5000 and has an age-related penetrance. The disease clinically affects males more frequently than females (up to 3:1), despite the same prevalence of carrier status between sexes, as would be expected for an autosomal dominant mode of inheritance (Pilichou et al., 2016). The natural history of ARVC is predominantly related to ventricular electrical instability, which may lead to arrhythmic SCD, progression of ventricular involvement, and heart failure (Corrado et al., 2015).

Genetics of ARVC

ARVC is a genetically transmitted disease. Although the genetics for ARVC follow Mendelian

rules, the situation is made complex due to variable expressivity and potentially reduced penetrance (Read & Donnai, 2015). A familial background consistent with an autosomal-dominant mode of inheritance is usual.

Occasionally a clear family history is not obvious, but this is likely due to incomplete family histories, the variable expressivity of the disease and potential misattributed parentage. In a person with an autosomal dominant mutation, there is a 50% chance they will pass the disease to their offspring (Merner et al., 2008). There is plenty of intrafamilial variation regardless of the type of ARVC and/or location of the mutation (Merner et al., 2008). Causative mutations have been described in both desmosomal and non-desmosomal proteins (Pilichou et al., 2016).

There are several genes associated with the ARVC phenotype, the majority of which to date are desmosomal. Desmosomes are a complex formed by proteins and function to bind the myocardial cells to each other; they are vital for electrical conduction and mechanical contraction in the heart cells. The most studied desmosomal genes involved in the genetics of ARVC are the junctional plakoglobin (JUP), plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), and desmocollin-2 (DSC2). These cause different forms of ARVC disease, most of which are autosomal dominant, with the exception of Naxos disease which is caused by homozygous mutations in JUP (junctional plakoglobin) and Carvajal syndrome caused by homozygous DSP (desmoplakin) mutations. Desmosomal genes identified for ARVC include TGFB3 (causing ARVD1), RYR2 (causing ARVD2), TTN (causing ARVD4), and DES (causing ARVD7). Other causative

genes include PLN, LMNA, SCN5A and CTTNNA3. Furthermore, some causative genes are yet to be found (ARVD3 and ARVD6 loci) (Ohno, 2016).

One such non-desmosomal mutation was identified (the ARVD5 locus (MIM 604400) on chromosome 3p) and mapped in an extended eight-generation family from the genetically isolated population on the island of Newfoundland, Canada in the 1990s (OMIM®, 2013). *TMEM43* is a gene located on chromosome 3p25, in which the mutation p.S358L causes the common ARVC phenotype present in the NL population. The first family was identified in the late 1970s due to the high occurrence of SCD. However, the location of the ARVD5 gene was not known until 1998, and the gene itself and the causative mutation was not discovered until 2008. A missense mutation in the *TMEM43* causes a fully penetrant, sex-influenced lethal form of ARVC (Merner et al., 2008).

For clarification, the term ARVD was used first in the literature related to this patient population. Subsequently, the term ARVC became more commonly used, followed by ARVC/D to encompass a wider range of pathophysiology. Currently, the simplified term of arrhythmogenic cardiomyopathy is becoming more widely used for this family of disorders. Mendelian Inheritance in Man (MIM, or its online equivalent OMIM) is a compendium of human genes and genetic phenotypes that has been collated since the 1960s. It contains cumulative information with little editing. The first locus for ARVC was determined when the disease was still referred to as ARVD (prior to 1996), so all loci (the position on a chromosome) in OMIM use that

nomenclature (ARVD1,2,3….etc). As the specific gene at each locus was discovered (e.g., *PKP2* is found at locus ARVD9, *TMEM43* is found at locus ARVD5), the locus position name became redundant. The disease (ARVC) is caused by a mutation (of which there can be several) within a gene (of several genes), that causes ARVC. This thesis focuses on ARVC caused by the p.S358L mutation in *TMEM43*, the locus for which is on the short arm of chromosome 3 and is known within the OMIM nomenclature as ARVD5.

Symptoms of ARVC: clinical presentation

ARVC is phenotypically variable, with wide clinical expression including subtle right ventricular structural changes, ventricular tachyarrhythmias, palpitations, dizziness, syncope, heart failure, and SCD. The first and final clinical manifestation can be SCD (Sattar Y., Abdullah H.F., Samani E.N., Myla M., Ullah W., 2019). Many ARVC patients can remain clinically asymptomatic for decades, making the condition difficult to diagnose. However, symptoms of the disease usually present in the second to fourth decades of life with evidence showing overall greater clinical severity in males (Choudhary et al., 2016).

The natural history of ARVC is predominantly related to ventricular electrical instability and dysfunction, life threatening events which can lead to SCD (Corrado et al., 2015). Prognosis is highly dependent on various factors, including the genetic subtype of ARVC, the rate of disease progression, sex, and treatment modalities used. Tragically, many sudden deaths occur in young

adults and vigorous activity is believed to be a risk factor for SCD (Paulin et al., 2020). However, it can also occur in the absence of physical activity. The incidence of SCD ranges from 0.08% to 3.6% per year in adults with arrhythmogenic cardiomyopathy (Basso et al., 2018). The mechanism of SCD in ARVC is cardiac arrest due to electrical instability of the heart, causing sustained ventricular tachycardia (VT) leading to ventricular fibrillation (VF) (Corrado et al., 2015).

ARVC due to p.S358L in *TMEM43* is a virulent form of ARVC with extreme variability of expression. A particular set of clinical characteristics is observed in this patient population. Males present with a more malignant phenotype, with earlier age of onset of cardiac symptoms and SCD as compared to females. Females are more likely to present with syncope and palpitations, and have fewer hospitalizations. Symptom onset in females is usually delayed by 1-2 decades. Other clinical features include poor R wave progression (PRWP), left ventricular enlargement (LVE), and ventricular ectopy on Holter monitor (Hodgkinson et al., 2013). In affected subjects in the NL population, 86% of males presented with SCD vs 42% of females (Merner et al., 2008).

Diagnosis of ARVC

ARVC is genetically and clinically heterogenous and thus is difficult to clinically recognize and diagnose as it can resemble other cardiac conditions (Hodgkinson et al., 2013). High clinical and genetic variability is reported.

The diagnosis of ARVC does not rely on a single gold standard test but is achieved using a scoring system, proposed in 1994 and updated in 2010 by an International Task Force, which encompasses familial and genetic factors, histological features, ECG abnormalities, arrhythmias, and structural/functional ventricular alterations (Silvano et al., 2016). Diagnostic tests include electrocardiographs (also known as ECGs), Holter monitors, echocardiograms, cardiac magnetic resonance imaging (MRIs or CMRs), cardiac biopsies, and genetic mutation analyses.

The most important 2010 update has been genetic mutation testing (Marcus, Edson, & Towbin, 2013). The updated criteria included three diagnostic levels: a definite diagnosis (two major criteria or one major and two minor criteria or three minor criteria); a borderline diagnosis (one major and one minor criteria or three minor criteria); and a possible diagnosis (one major criteria or two minor criteria).

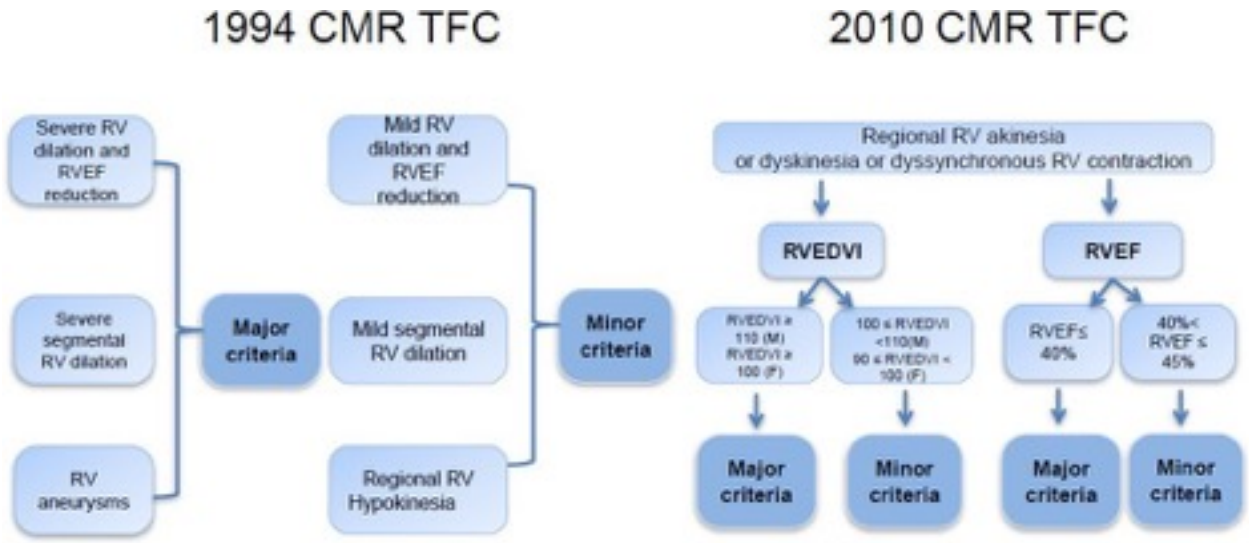

Figure 2.1: The 1994 and updated 2010 ARVC CMR Task Force criteria

From: Effect of the 2010 task force criteria on reclassification of cardiovascular magnetic resonance criteria for arrhythmogenic right ventricular cardiomyopathy.

The flow diagram shows comparison of the details for 1994 and 2010 ARVC CMR criteria.

ARVC=Arrythmogenic Right Ventricular Cardiomyopathy; CMR= Criteria for Magnetic Resonance; TFC= Task Force criteria; RVEDVI= Right ventricular Ejection dysfunction; RVEF=Right ventricular ejection fraction; RV=Right ventricle

Generally, ARVC patients who meet the Task Force Criteria (TFC) for ARVC are at a high risk for SCD (Azaouagh, Churzidse, Konorza, Erbel, 2011). Use of the TFC has proven a challenge in several clinical populations, including the ARVC population in NL. Some of the challenges encountered include geographical restraints, unavailability of testing instruments in rural areas of the province and the need to have overt clinical disease presentation to be eligible for testing. The TFC are used as a baseline for a diagnosis of the ARVC condition. However, given the multiple challenges of using the criteria in various populations, it represented the NL ARVC cohort poorly. This cohort has been diagnosed largely based on genetic testing instead. Thus, diagnosis is easier since the introduction of genetic testing and the discovery of the *TMEM43* p.S358L mutation.

In NL, the p.S358L *TMEM43* subtype is a particularly lethal form of ARVC. The positive

TMEM43 p.S358L mutation alone constitutes diagnosis in the absence of any clinical abnormality (thus very different to the usual diagnostic TFC described above). This is due to the work on the NL families which, clearly delineate the natural history such that we know SCD can be, and often is, the first clinical presentation. Therefore, anyone with or without affected relatives can be tested for this variant in *TMEM43* and get a diagnosis.

Due to the difficulties encountered with the TFC mentioned above, the NL ARVC cohort was examined using a different, distinct set of criteria, especially designed to capture this unique population. The criteria used for the NL ARVC population identify three levels of clinical status based on clinical history and genetic testing results: affected, unaffected, and unknown. Detailed information on the criteria are presented in Table 2.1: (Hodgkinson et al., 2005; Merner et al., 2008).

Table 2.1: TMEM43 p.S358L ARVC clinical status factors

Clinical Status	Criteria
Affected (one of the following criteria required)	Obligate carrier*
	SCD under 50 years old
	Cardioversion** for VT or VF <50 years old
	Genetic diagnosis: gene mutation (*TMEM43*, p.S358L) positive
Unaffected	Gene mutation (*TMEM43*, p.S358L) negative

Clinical Status	Criteria
Unknown	Do not fulfill criteria for affected or unaffected (eg. no gene mutation screening results available

*obligate carrier status= has a clinically affected parent and a child; must carry the gene mutation based on analysis of the family history (Merner et al., 2008)
**cardioversion= refers to a medical procedure by which an abnormally fast heart rate (tachy-cardia) or other cardiac arrhythmia is converted to a normal rhythm using electricity or drugs (“Cardioversion,”May 8, 2020)

ARVC in NL; ARVC caused by p.S358L in TMEM43

A rare, lethal subtype of ARVC exists on the island of Newfoundland linked to a p.S358L missense mutation located within the *TMEM43* gene. A heterozygous amino acid substitution (p.S358L) in *TMEM43* fully co-segregated with autosomal dominant ARVC, and thus was shown to be a founder mutation on the island of Newfoundland (Canada) (Milting et al., 2015; Merner., et al, 2008).

A founder effect is a reduction in genetic variability that occurs when a population is derived from a small number of colonizing ancestors (Teare, 2011). In NL, this is considered to be 20-30000 settlers. The *TMEM43* p.S358L ARVC subtype can be reliably traced to a single founder pair born in 1799 and 1800 (Hodgkinson et al., 2013). The comparably high incidence of *TMEM43* p.S358L ARVC in NL might be related to the genetic drift of this unfavourable variant

in larger populations (Milting et al., 2015). There is certainly evidence that the *TMEM43*-p.S358L mutation was imported by immigrants from continental Europe as there are several families with the exact same mutation (on the exact same background DNA haplotype) in Northern Germany and Denmark (Milting et al., 2015).

ARVC was first identified in the NL population in the late 1970s when a patient was identified with a known family history of SCD (Guiraudon et al., 1983). The descendants of this patient are still being seen, diagnosed, counselled and treated in NL. The first NL family with ARVC was reported in 1988 (Marshall et al., 1988). This same eight-generation family was used to map the ARVD5 locus (MIM604400) in 1998 (Ahmad et al., 1998). This study identified a linkage to chromosome 3 and a disease-associated founder haplotype at locus ARVD5 was recognized. A haplotype is a series of linked genetic markers surrounding the gene locus, which are inherited together in affected individuals across generations. In 2007, the causative mutation was found in a novel gene *TMEM43* within the disease-associated founder haplotype. The research team was then able to identify families with the founder mutation and obtain medical records, and analyze relevant cardiac outcomes based on the haplotype finding. This is how the secondary database of clinical and demographic information began. The research also demonstrated that this genetic subtype of ARVC is lethal with a median age to death in men of 41 years compared to 71 years in women and the disease is 100% penetrant (Hodgkinson et al., 2009). Despite the sex influence, the disease follows a classic autosomal dominant mode of inheritance with clear male-to-male transmission.

Since then, 27 Newfoundland families are confirmed to share the ARVD5 haplotype. One such family pedigree alone comprises 1200 individuals spanning 10 generations (family 64). The mutation represents 0-2% of all known ARVC mutations, but is found in much higher proportion on the island of Newfoundland. The potentially high prevalence of the subtype of ARVC in NL is believed to be a genetic founder effect.

A cardiomyopathy genetics research clinic was initiated in NL in 1998 following genetic investigations allowing an American research team to link two families with ARVC in NL to chromosome 3p25 (Ahmad et al., 1998). Local genetic testing began at that time and serial data (retrospective and prospective) on subjects born at *a priori 50%* risk were collected. At *a priori 50%* risk means being at a 50% risk at baseline (birth) of having the *TMEM43* p.S358L mutation, based on one of your parents carrying the mutation. This subsequently paved the way to the discovery of the ARVC disease causing p.S358L mutation in the *TMEM43* gene discovered by Merner and colleagues in 2008.

This is a form of ARVC with extreme variability of expression and is sex influenced. Onset of cardiac symptoms, clinical events, and test abnormalities occurred in affected males significantly earlier as compared to affected females. Survival is significantly reduced with a median survival of 41 years vs 83 years in the normal population and the relative risk of dying in males is 6.8x greater than in females (Merner et al., 2008). This particular type of ARVC has a higher mortality rate and a markedly reduced life expectancy as compared to other familial forms of ARVC. It

reaches 100% penetrance in affected individuals, meaning that all individuals with the *TMEM43* p.S358L mutation will develop symptoms of the disease at some point in their lifetime (Merner et al., 2008).

Therefore, it is clear that the ARVC caused by a p.S358L mutation in *TMEM43* described in NL families is a subtype with severe clinical manifestations, is sex-influenced and causes premature death. This is a uniquely homogenous ARVC population that can provide vital and robust details about this disease in ways that variable heterogenous populations cannot. This is also a group that has been studied extensively since 1998 and can provide ongoing insights into the characteristics of this disease process.

Clinical management of ARVC

The most important objectives of clinical management in ARVC patients include the following: reduction of mortality (from SCD, arrhythmia and heart failure), prevention of disease progression leading to ventricular dysfunction and heart failure, improving QOL, and increasing functional capacity. These interventions have the potential to change the natural history of the disease (Romero et al., 2013).

Individuals with ARVC require lifelong clinical monitoring and management comprising various treatment modalities, including lifestyle, pharmacological, and mechanical interventions.

Although there is a growing knowledge base around ARVC outcomes and risk factors, rigorous evidence on how to treat this patient population is still lacking due to the relatively low disease prevalence and the absence of controlled studies (Corrado et al., 2015). The main challenge is to improve risk stratification for better identification of high-risk patients for SCD and heart failure.

Regular cardiac monitoring includes ECGs, Holter monitors and echocardiography to follow disease progression. Lifestyle modifications include limitations to physical activity to reduce the risk of arrhythmias and SCD (Romero et al., 2013). Pharmacological options include antiarrhythmic drugs such as amiodarone, sotalol, other beta blockers, and ACE inhibitors. The mechanism of action of such drugs includes decreasing the workload on the heart by suppressing heart muscle stimulation and slowing the electrical impulses of the heart (Levine, 2020). However, there is little evidence that activity restriction and medications improve survival or alter the natural history of the disease (Guttmann, Mohiddin, Elliott, 2014). Data shows that the majority of life-saving ICD interventions in high-risk patients occurred despite concomitant use of antiarrythmic agents.

The most important and most widely accepted non-pharmacological treatment modality for the prevention of SCD is the ICD. Since 1984, the ICD has been used in primary prevention of sudden death (Rahmawati et al., 2013). Its evolution into the pacemaker-sized device placed in the upper chest that we see today took several prototypes, envisioned by the pioneering cardiologist Michel Mirowski in the late 1960s (Deyell, Tung, & Ignaszewski, 2010). The ICD works by

normalizing an irregular heartbeat. It monitors the heart rhythm and generates electrical shocks if the rhythm errs too far from normal, essentially restoring a normal heart rate and rhythm. In ARVC patients, the device is used for primary or secondary prevention and has been proven to save lives (Corrado et al., 2015). Primary prevention means the prophylactic implantation of the ICD for asymptomatic patients, usually individuals known to be at high risk of SCD given their family histories or ARVC genetic subtype. Secondary prevention is for patients who have experienced arrhythmias or other cardiac complications (such as a cardiac arrest) prior to the ICD implantation (Romero et al., 2013). A significant decline in mortality rates due to SCD from potentially fatal ventricular tachyarrhythmias has been attributed to ICD implantation (Hodgkinson et al., 2005).

Guidelines for the prophylactic use of ICD in ARVC are not generally established (however, they have been established for the unique *TMEM43* p.S358L population in NL). However, ICD therapy is considered the first line approach for the highest-risk patients, whose natural history is typically characterized by the risk of SCD (Pilichou et al., 2016). The available data from observational studies of large populations of ARVC patients have established efficacy and safety of ICD therapy. Studies consistently document that the ICD successfully interrupts lethal ventricular tachyarrhythmias and improves long term outcome of patients (Pilichou et al., 2016). The largest such single centre trial of its kind found an estimated improvement of overall survival rates of 23% after 1 year, 32% after 3 years, and 35% after 7 years. This was complemented by other observational studies that showed rates of life-saving ICD interventions in 30-50% of

patients during follow up. Of note, most of the interventions were >1 year after implantation. The ICD showed favourable outcomes and terminated up to 91% of the hemodynamically stable VTs in patients (Corrado et al., 2015). Patients who meet the TFC for ARVC are at high risk for SCD and should undergo ICD placement for primary and secondary prevention, regardless of electrophysiologic testing results (Azaouagh et al., 2011).

Special considerations in the Newfoundland TMEM43 population

The p.S358L *TMEM43* subtype of ARVC is a malignant disease; therefore, ICD use in the NL ARVD5 population is largely done for primary prevention (Hodgkinson et al., 2005). In this cohort, the use of the ICD was influenced by the fact that the presenting symptom often was SCD.

The 5-year mortality rate in this patient cohort was zero for those with an ICD compared with 28% in control subjects (p= 0.009) (Hodgkinson et al., 2005; Azaouagh et al., 2011). In addition, within 5 years, the ICD fired for VT 70% and for VT >240 beats/min in 30% with no difference in discharge rate when analyzed by ICD indication. More recent data suggests an even more dramatic benefit of the ICD. Twenty-four multiplex families with the fully penetrant form of the ARVC subtype were followed for 20 years. Of note, the *TMEM43* p.S358L phenotype is modified by sex. The median age of death in untreated males is 41 years and in females 67 years, due primarily to sustained VT/VF. Males who received an ICD for primary prophylaxis (PP) had a 5-year survival rate of 95% compared with 65% in controls; males who received the ICD for

secondary prevention (SP) had a 5-year survival rate of 100% compared to 50% in controls. The 5-year cumulative incidence rate of discharge for the PP males was not significantly different from the 5-year mortality rate in the PP control group, whether for VT at any rate or for VT/VF (>240 beats per minute); in the SP males, this was the case for the cumulative rate of discharge for VT/VF. The comparison was less dramatic in females. Because of the sex influence of the disease on the natural history, those who received the ICD for PP had a 5-year survival rate of 97% compared with 85% in controls (Hodgkinson et al., 2016).

International guidelines state (according to TFC) that gene carriers who have no cardiac phenotype should not get an ICD (overt clinical cardiac disease is required to be eligible). The most recent task force consensus statement on treatment for ARVC defines the ICD as being indicated in high-risk patients after sustained VT/VF. However, in the *TMEM43* p.S358L population, previous reported outcomes showed statistically significant survival benefit for males, regardless of presentation. Notably, decreased mortality was observed despite the fact that most subjects received an ICD before the documented onset of ventricular arrhythmias. The Hodgkinson et al., 2016 clinical data clearly supports an ICD discharge as being a death event in the absence of the ICD. The study adds to the literature in support of ICD treatment as a primary prophylaxis based on genotype alone for the genetic subtype of ARVC caused by *TMEM43* p.358L because it provides a significant survival advantage.

The results of Hodgkinson et al. (2005) supported prophylactic ICD implantation as a primary

prevention therapy in familial ARVC with a high risk DNA haplotype (ARVD5, 3p25) and/or pedigree position with a beneficial impact on survival in this population. The Hodgkinson et al. (2016) study further supported ICD prevention, but now solely based on mutation screening, as it became available to the population. ICD therapy is therefore indicated for primary prevention in postpubertal males and females in their third and fourth decades with the p. S358L *TMEM43* mutation (Hodgkinson et al., 2005, 2016).

The conclusions from the clinical data strongly supported an indication for primary prevention ICD therapy in postpubertal males and in older females with the p.S358L *TMEM43* mutation. The clinical course created by providing asymptomatic *TMEM43* p.S358L mutation positive individuals with an ICD has changed the natural course of the disease tremendously. Long-term follow-up of the effectiveness of ICD therapy in ARVC families with a p.S358L mutation in *TMEM43* clearly shows that males obtain a significant and substantial survival benefit whatever the indication for ICD and that females obtain a significant, albeit smaller, benefit.

Specifics of the ICD

It is clear from available studies that ICD implantation is a lifelong preventative measure and is the only proven “lifesaving” therapy. This is specifically discussed above in reference to the *TMEM43* p.S358L mutation positive population. Nonetheless, some authors (Roston, Krahn, Ong, Sanatani, 2019; Matlock et al., 2011; Katritsis & Josephson, 2012; Gonzalez-Torrecilla et

al., 2015) suggest that the ICD is overused and its treatment potential should be more closely scrutinized. However, it is important to note that these studies are referring to general ARVC recipients of the ICD, and not our cohort in particular, whose natural history is clear and much more malignant as compared to other forms of ARVC. Despite its clear survival benefit in many populations (including the *TMEM43* p.S358L group), ICD complications need to be considered. These include device malfunctions, appropriate and inappropriate discharges, and lead related adverse effects. ICD interventions (discharges) are painful and can have an impact on psychological health. Many existing studies do not report adverse ICD outcomes, and observational data increasingly show that complications may be under-recognized in some patients (Roston et al., 2019; Winkel & Tfelt-Hansen, 2019).

In the homogenous p.S358L *TMEM43* NL population, ICD complications occurred in 2% of the patient cohort. Inappropriate discharges occurred in 27% of primary prevention males, 36% of secondary prevention males, and 18% of females. Almost 20% of the cohort had repeated appropriate discharges and 6% had repeated inappropriate discharges (Hodgkinson et al., 2016).

Furthermore, particularly in young patients, the lifetime risk of the ICD is not trivial. This is an important factor as the ICD leads to an increased lifetime risk of device-related complications and detriment to QOL (Romero et al., 2013). Furthermore, battery replacements for the ICD are needed, on average, every 10 years. The ICD may cause lasting psychiatric sequelae in a patient and the decision to pursue ICD therapy is a complex one.

Part Two: Mental health and the Implantable Cardioverter Defibrillator

Survey instruments to assess mental health in those with an ICD

There are currently no mental health instruments designed for use specifically in the ICD population. However, several instruments have been validated in chronic disease populations, with Cronbach alpha coefficient values above 0.70. These include clinician administered instruments such as the Beck Depression Inventory, the Geriatric Depression scale, and the Hospital Anxiety and Depression scale. The PHQ-9, SAS, and PCL-C scales chosen for our study have good reliability and validity across several health conditions, and due to this were well suited as instruments of measurement for our ICD population, as well as in family members (due to their general reliability and validity overall). Further discussion regarding the scales used in this study is available in the survey instruments section under Methods.

Psychiatric sequelae and ICDs in heterogenous cardiac populations

A link between cardiac disease and psychiatric sequelae has been established. There is less data on mental health effects related to treatment with the ICD, especially in patients with inherited cardiac diseases. Comparisons between patients with and without an ICD showed that anxiety and depression were prevalent in heart disease patients, including in those requiring an ICD (Magyar-Russell et al., 2011). It has been well documented that some ICD recipients experience

psychological distress and have difficulty adjusting to the device (Dunbar et al., 2012; Sears & Conti, 2006; Thomas et al., 2009). However, it is still unclear whether the appearance of new psychopathologies is due to the cardiac disease, the ICD implantation that follows, or the ICD shocks (Mauro, 2010).

A limitation in the risk stratification literature is that negative ICD outcomes are not systematically reported, leading to an over-estimation of net benefit. In some studies, ICD complications have been shown to be as high as 5.4% per year, including a 2.8% per year inappropriate shock rate (Roston et al., 2019). With the literature that is available, most publications do not differentiate between different types of harm, and few quantify the cumulative benefit of appropriate therapies versus the cumulative burden of harm (Roston et al., 2019). More ICD shocks also correlate to an increased severity of disease, so the higher the burden of shocks means the higher likelihood that it is saving lives. This conundrum can in itself have an effect on mental health. In addition, studies on this unique population rarely have good data on the natural history of the disease, which makes it more difficult to compare and contrast the benefits and harms of ICD therapy. In the NL population, the natural history of the disease is well delineated, and therefore can give us a reasonable comparison, demonstrating the ICD's clear lifesaving benefits.

Any medical intervention can have a lasting physical and mental impact on an individual. ICDs are designed to detect and terminate VT and/or VF via electric shock (defibrillation). When VT or VF is detected, electrodes implanted in the heart muscle discharge an electric shock in accordance with a predetermined program and revert the arrhythmia. Not surprisingly, this shock is

very uncomfortable. Depending on the severity of the arrhythmia and the state of perfusion, the patient can also be unconscious when the device shocks. Therefore, in spite of its function of saving lives, the ICD can cause negative emotional effects among patients (Rahmawati et al., 2013).

A study by Morris et al. (1991) was the first study conducted on psychiatric prevalence and ICD [seven years after the first ICD implantation]. The study examined patients 3-21 months post-implantation of an automatic ICD; 50% of patients exhibited some identifiable disorder including depression, panic disorder, and specific phobia. Since 1991, this area of research is still fairly limited and consists of mostly observational cohort studies and cross sectional studies. Studies have found the following disorders in the general ICD population: phobic anxiety, PTSD, panic disorder, somatoform disorder, agoraphobia, and depression, and lower QOL scores. According to the available literature, patients with an ICD require greater emotional attention due to the imminent risk of SCD.

The ICD and depression and anxiety

According to the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM5), symptoms of depression include greater than two weeks of five or more of the following symptoms: depressed mood, diminished interest or pleasure, weight changes, insomnia or hypersomnia, psychomotor agitation or retardation, energy loss, feelings of worthlessness or excessive in

appropriate guilt, diminished concentration, and suicidal ideation. Presentations and distress levels can vary with each individual (American Psychiatric Association, 2013). According to Statistics Canada, the lifetime and 12-month prevalence of major depressive disorder (MDD) in Canada is 12.6% and 4.7%, respectively. The prevalence of depressive symptoms not meeting criteria for a disorder is difficult to estimate but considering 1 in 5 individuals are impacted by a mental illness at any given time, we can estimate that it could be upwards of 20% (Statistics Canada, 2020). A meta-analysis of over 5000 ICD-implanted patients estimated a 20% prevalence rate of depressive and anxiety symptoms- a rate not different from that in cardiac populations without an ICD (Carroll & Hamilton, 2005).

Symptoms of anxiety present in a variety of manifestations, including [but not limited to] phobias, social anxiety, panic attacks, and generalized anxiety disorder. Generalized anxiety disorder (GAD) is the most common anxiety disorder, with a lifetime and 12-month prevalence of 8.7% and 2.6%, respectively. Subclinical anxiety symptoms are even more common. Symptoms associated with anxiety can include excessive worry, restlessness, fatigue, difficulty focusing, irritability, muscle tension, and sleep disturbance. Other symptoms include panic attacks and agoraphobia. Presentations can vary among individuals and affect functioning in different ways.

Clinically relevant anxiety has been reported in up to 38% of patients in some ICD studies, with even higher reports of subclinical anxiety symptoms. This usually constitutes anxiety that has a noticeable effect on an individual's functioning, and can manifest with dysfunction in the work

place or at home. Up to 30% of ICD patients also develop depression. Not surprisingly, a significant reduction in QOL has also been noted (Thylen et al., 2015).

Previous studies have delineated a possible association between mood disturbance and arrhythmia events in patients after ICD implantation (Thylen et al., 2015). It is unclear as to what may increase the risk of these disorders in a substantial minority of patients, but female sex, younger age of ICD implantation, and shock frequency have been implicated.

Hoogwegt et al. (2012) found that 35.5% of ICD patients were emotionally distressed at baseline, 70.2% of whom received no psychological treatment. There was only a slight improvement at 12-month follow up, with 24.3% of all patients with clinically significant levels of distress. Emotional distress was measured. Those patients that experienced distress but had no treatment reported a significantly poorer health status on the Short Form Health Survey (SF-36) at 12-months compared to those without emotional distress ($p<0.001$).

Dunbar et al. (1999) observed that depression and anxiety in individuals affected the functioning of the device. Van den Broek et al. (2013) also looked at the connection between emotional distress and how it affected mortality rate in patients with ICDs. The authors found that negative affect increased mortality rate even when controlling for confounders. Negative affect described individuals with what is known as a Type D personality, which refers to a general propensity to psychological distress that is defined as a combination of negative affectivity and social

inhibition (inhibition of the expression of negative emotions). The study focused more on the psychological profile of the patients rather than demographic or clinical factors.

A longitudinal study by Mauro et al. (2010) assessed the uncertainty and psychological adjustment of having an ICD over time. In this study, uncertainty regarding the illness process and having an ICD was measured by the Mishel Uncertainty in Illness scale (MUIS); psychosocial adjustment was measured by the Psychological Adjustment to Illness Self-Report (PAIS-SR). Participants had ICDs for secondary prevention purposes and were predominantly older males (average age 70 years old); the mortality rate for the study was high at follow up (44%). Participants were investigated for psychological adjustment to the device at 1 and 8 weeks following an initial ICD implant. The study found psychiatric distress was frequently seen prior to an ICD, and early adjustment to the device (in the first 2 months) explained 40% of the variance in overall adjustment long-term. The authors suggested screening for psychiatric sequelae prior to implantation, something that is rarely done in practice.

However, several studies found no change, or even improvement, after ICD use. Leosdottir et al. (2006) measured health-related QOL, anxiety and depression in patients with an ICD compared to that of pacemaker patients and found no differences among the two groups. A study by Carroll et al. (2002) similarly reported no change in psychiatric symptoms or QOL in ICD recipients at baseline and 6-month and 12-month follow up. Arnous et al. (2011) investigated the effectiveness of the ICD in 71 patients and QOL. They found a low complication rate and high level of

tolerability of the device. Unlike the other studies described, the population in the Arnous study was explicitly given an ICD for prophylactic purposes for the primary prevention of SCD. Lemon et al. (2007) found positive psychological adaptation rather than psychiatric decline after an ICD. Furthermore, a later study by Carroll et al. (2008) looked at the long-term effects of ICDs on health status, QOL, and psychological state over a four-year timeline using a prospective longitudinal design of 30 ICD patients. Psychological state tended to improve after 6 months but then declined again after 3-4 years. It is important to note that the participants in these studies had ICDs for various reasons and ICDs for ARVC recipients were not explicitly mentioned. Also, the mean ages of participants were above 60 years old.

Amiaz et al. (2017) wanted to identify new onset mental illness after ICD implantation for predominantly primary prevention: 158 outpatients with a mean age of 64 years were included with many different indications for the device, but all considered high risk patients. Using the Hamilton Anxiety scale (HAM-A) and Hamilton Depression scale (HAM-D) to measure symptoms of depression and anxiety, the authors found that 28% of patients had depressive symptoms at baseline. The rates of MDD found in the study were fairly consistent with that found in cardiac populations. Symptoms improved one year after implantation (Amiaz et al., 2017).

Possible effects of age, sex, and shocks

Female sex is thought to be an independent risk factor for psychiatric sequelae in the ICD

population. Prior studies have specifically identified younger female recipients to be at a higher risk for future adverse psychological consequences and QOL impairment (Rahmawati et al., 2013). However, this has not been well delineated in the literature as most studies to date have included predominantly males (Bostwick & Sola, 2007). Versteeg et al. (2017) conducted a study with 241 patients (of whom 33% were women) who received an ICD for the indication of heart failure. The study found that females reported more symptoms of anxiety and somatic health complaints; age was also implicated as a risk factor, with younger ages (<60 years old) having potentially more difficulties adapting to the ICD device.

Rahmawati et al. (2013) studied a more elderly population with ICDs given for secondary prevention for heart failure and reported that women had poorer QOL scores, specifically for physical functioning and bodily pain, as compared to men. Significant relationships were found between the sexes and depression, ICD and PTSD, but not anxiety. Overall prevalence for depression, PTSD, and anxiety were 16.8%, 23.5%, and 27.9%, respectively (Rahmawati et al., 2013). In contrast, Brouwers et al. (2011) found that female sex was statistically significantly associated with increased anxiety.

Fears around ICD shocks have been identified as a major determinant for psychological distress. In patients with an ICD, ICD shocks might lead to the development of new anxiety or depression symptoms (Beery, Baas, & Henthorn, 2007; Bilge et al., 2006; Carroll & Hamilton, 2008). Some studies have observed a connection between these disorders and the number of ICD shocks a

patient receives. Other studies have pointed to having concerns about receiving shocks, but not shocks themselves (Thylen et al., 2016). A significant percentage of patients who have ICDs experience a shock in the first year after implantation, ranging between 10-54% (de Ornelas Maia, Soares-Filho, Pereira, Nardi, & Silva, 2013). Activation of the ICD device (if the patient remains awake) is unpredictable and painful, being described as 'a kick in the chest by a horse'. The shock is a very unpleasant experience for the patient, and can cause avoidance of working situations, physical exercise, and sex, because the patient associates these activities with the occurrence of electrical discharges (Maia et al., 2014).

Early studies reported associations between the frequency of ICD shocks and anxiety (Bostwick & Sola, 2007; Passman et al., 2007; Carroll & Hamilton, 2005; Bilge et al., 2006; Van den Broek, Nyklicek, Van der Voort, Alings, & Denollet, 2008). Anxiety and depression following the first shock were found to be the most common psychiatric disorders in observational studies and clinical trials. Other studies found no such associations (Crossmann, Pauli, Dengler, Kuhlkamp, & Wiedemann, 2007; Keren, Aarons, & Veltri, 1991; Piotrowicz et al., 2007). There has been some debate as to whether anxiety is a precursor or a consequence of ICD therapy. Recent reviews have concluded that the risk of anxiety with increased shocks may indeed be associated, but not as strongly as previously thought (Schultz et al., 2013).

Jacq et al. (2009) evaluated 40 patients with ICDs, dividing those patients who had experienced at least one shock from those who had not. Using the Mini International Neuropsychiatric Inter

view (MINI), the Hospital Anxiety and Depression scale (HADS), and the SF-36, the researchers found that 37.5% of those who had experienced a shock had an identifiable anxiety disorder, compared to only 8% in the group who had not experienced a shock. Similarly, the prevalence of depressive disorders in the group that experienced at least one shock was 50%, as compared to 23% in the control group (P= 0.04).

Redhead et al. (2010) conducted a survey on the prevalence of anxiety and depression among 106 patients three years after ICD implantation for secondary prevention following myocardial infarction. The ICD group was compared to three control groups matched for sex and age: a pacemaker group, a percutaneous coronary intervention group (PCI), and a group with atrial fibrillation that had undergone catheter ablation. Anxiety and depression, and QOL were measured using the HADS and SF-36. Mean scores on the scales were similar between the groups, with all groups scoring high on anxiety measures, and within normal limits on depressive symptoms, with prevalences in the ICD group ranging from 11-13% and 5-8%, respectively. The ICD group with no shocks had a prevalence of anxiety of 14%, which was largely similar to control groups. In comparison, the ICD group who experienced shocks had a statistically significant anxiety syndrome prevalence of 26%; those who experienced shock storms (≥3 shocks in 24 hours) met HADS criteria for positive anxiety syndrome 64% of the time (Redhead, Turkington, Rao, Tynan, & Bourke, 2010).

Thylen et al. (2016) investigated the connection between anxiety and depression and

defibrillating shocks from the ICD. They found that the association between the receipt of shocks and psychological distress was mediated by high ICD-related concerns and therefore these concerns played a strong role in the development of potential anxiety and depression. Patients with more psychological distress were more likely to be relatively younger females who had received one or more ICD shocks, and were more likely to receive the ICD for secondary (rather than primary) prevention. Anxiety scores were strongly correlated to depression scores and ICD concerns.

Godemann et al. (2004) investigated the prevalence of anxiety disorders using the standardized lifetime Diagnostic Interview of Psychiatric Syndromes (DIPS) assessment tool in 90 patients with an ICD and found 16.7% of these patients developed anxiety disorders after the impact of a shock from ICD implantation. The more shocks they had, the greater their anxiety and depression ($P<0.001$).

Schultz et al. (2013) examined the temporal contingency of anxiety and ICD therapy in patients with ischemic heart disease. In a prospective, longitudinal study, 54 patients receiving the ICD for the first time were assessed for anxiety at baseline and at 12-month follow up using a variety of scales and diagnostic tools (the Spielberger State Trait Anxiety Inventory-STAI, the Beck Anxiety Inventory- BAI, the Beck Depression Inventory- BDI, the Fear Questionnaire-FQ, and the Panic and Agoraphobia Scale-P&A). Importantly, scale completion was followed by a DSM-IV Structured Clinical Interview (SCID) to screen for all anxiety disorders; this would be

considered the gold standard in assessment of any anxiety disorder. Results showed that anxiety prior to receiving an ICD did not predict the number of shocks or anxiety post ICD. However, increased shocks significantly predicted anxiety post ICD implantation even after controlling for confounders of age, sex, cardiac health and baseline depression (BAI results); in particular, symptoms related to panic and GAD. Of note, this sample population had an unusually high shock rate, with over 50% of patients experiencing five shocks or more within the one year follow up period. Furthermore, higher shock frequency predicted increased depression and anxiety and emerged as a risk factor for panic and agoraphobia.

ICD and posttraumatic stress

Most available studies to date have focused on anxiety and depression. Much less is known about levels of posttraumatic stress and its effect on this population. Posttraumatic stress disorder symptoms generally fall under three symptom clusters. Diagnosis of the disease requires exposure to threatened death or serious injury or it had to have happened in a close family member or friend. These include the following symptoms: re-experiencing aspects of the trauma (in this case the traumatic cardiac event) or intrusive thoughts about the ICD discharging; avoidance of activities associated with ICD firing, hyperarousal that can present as insomnia or irritability, and negative alterations in cognition and mood (American Psychiatric Association, 2013). The prevalence of the disorder in the general population is estimated at 8% lifetime and a 3.5% 12-month prevalence, with subclinical symptoms not meeting criteria believed to be higher.

Patients with an ICD may be particularly prone to develop PTSD symptoms, due to the ICD device acting as a constant physical reminder of their illness and the ICD's electrical discharge unpredictability. In addition, little is known about PTSD in younger patient cohorts, or those who experience multiple shocks, whether appropriate or inappropriate (von Kanel, Baumert, Kolb, Cho, & Ladwig, 2011).

Marshall et al. (2012) performed a prospective study on 47 patients who had an ICD for 12 months in relation to their QOL and anxiety. Symptoms consistent with posttraumatic stress severity (such as activity avoidance and alterations in mood and cognition) and anxiety related to the ICD device appeared to increase from baseline to follow up, with 19% of patients meeting criteria at both baseline and follow up assessments. Assessment between 2 and 5.5 years revealed increased chronic PTSD and another 20% had acquired new PTSD symptoms.

Habibovic et al. (2017) examined the trajectories of 249 ICD patients and associations with PTSD and anxiety symptoms. A younger age, an increased depression score at baseline and a negative personality (negative thinking) were all associated with increased vulnerability for posttraumatic stress and anxiety symptoms. Comparable trajectories were found for both symptoms of PTSD and anxiety.

von Kanel et al. (2011) assessed chronic posttraumatic stress attributable to a traumatic cardiac event and its predictors in 107 ICD patients. Increases in posttraumatic stress were found from

baseline (12%) to follow up (18%). Being female, helplessness, and depression predicted greater posttraumatic stress at baseline. Greater baseline posttraumatic stress, helplessness, alexithymia, experiencing greater than five shocks, and lower educational attainment (no graduation/primary school only) all predicted higher posttraumatic stress at follow up.

Kapa et al. (2010) studied 308 patients who had been implanted with an ICD and found that 223 of them developed anxiety disorders as well as PTSD. The frequency of PTSD declined over time from approximately 35% at baseline to 15% at both 6-and 12-month follow up ($P < 0.01$). Patients who experienced shock storms had significantly higher baseline PTSD scores (29.6%) based on the Impact of Events scale-revised (IES-R) version ($P < 0.01$).

ICDs in ARVC patients

Most available mental health data on ICD populations is heterogenous and focuses on those with ischemic heart disease. There is little data available on inherited cardiac disease and ICDs, and even less so in the ARVC population. In addition, knowledge of pre-ICD psychological profiles is scant (Gostoli et al., 2016). Psychiatric outcomes and mental health sequelae of these patients remain largely unexplored (Rhodes et al., 2017).

Available research shows that ICDs prolong survival in ARVC patients at high risk of SCD. ICD is a key treatment option for both primary and secondary prevention of SCD. Despite this, there

are a growing number of studies showing that the ICD is often associated with post implantation deleterious psychosocial effects, even in the absence of medical complications.

There are many factors that can affect the mental health of ARVC patients. These include non-pharmacological and pharmacological management modalities including physical activity restrictions, pharmacological drug therapy, and ICD implantation (Rhodes et al., 2017). Clinically significant psychiatric sequelae, such as symptoms of anxiety, depression and posttraumatic stress may hinder the survival benefits of the ICD. ARVC patients must adjust to the impact of living with a heritable condition and accept the difficulties of living with an ICD device.

Living with arrhythmias and the threat of ICD shock represents an ongoing challenge for patients to prepare and recover. Patients with ARVC may be at a particularly high risk for adverse outcomes for several reasons. Firstly, individuals with ARVC present at a younger age relative to others with ICDs. Previous studies have suggested that young age may be a risk factor for psychological maladjustment (Versteeg et al., 2017; Rahmawati et al., 2013; Thylen et al., 2016). Second, a high frequency of defibrillator discharge is often related to increased anxiety and poor adjustment. Individuals with ARVC, especially with a high-risk variant of the disease, have a high discharge rate. Some data shows upwards of 50-80% appropriate ICD discharge rate for treatment of sustained ventricular arrhythmia during a mean 3-5 year follow up period (Rhodes et al., 2017). Thirdly, in most ARVC populations there tends to be a higher proportion of women as compared to typical ICD populations in which more men tend to be affected (cardiac disease

populations). Women are considered to be at higher risk for poor ICD-related adjustment because of the overall higher risk of depression and anxiety prevalence in females. However, on the contrary, in the *TMEM43* p.S358L population, more males are affected and the disease is more malignant in males. Finally, patients with ARVC may be at particularly high risk for psychosocial problems because ARVC is a genetic disease. The disease etiology itself raises psychological burden, such as anxiety around risk to family members (particularly children), guilt, blame, and stigmatization (Etchegary et al., 2017; Van den Broek, Heijmans, & Van Assen, 2013). All of these circumstances and risks combine in patients with ARVC, and there is no gold standard as to how to identify those patients who may be at highest risk.

ICDs in ARVC: depression and anxiety

Limited studies explore mental health sequelae specifically in the ARVC patient population. The few studies available focus on general psychological adjustment and QOL.

Rhodes et al. (2017) did a cross sectional study on QOL outcomes in a heterogenous sample of 159 ARVC patients. The authors found that ARVC patients reported lower physical and mental QOL compared to a normative US sample, but higher scores as compared to an ICD sample (that received ICD for primary or secondary indications). Age also played a factor, with ARVC patients aged 18-35 reporting significantly lower mental health and QOL than older patients. Increased frequency of shocks also reported lower scores, and shock anxiety scores were

significantly higher among individuals who had experienced at least one shock. Female patients reported higher shock anxiety and lower QOL scores as compared to males.

James et al. (2012) undertook one of the first studies on psychosocial adjustment in patients with ARVC. They assessed psychosocial adjustment and associated risk factors using a cross sectional analysis with 86 patients ranging in age from 18-79 from the Johns Hopkins ARVD registry. Participants had a mean age of 45.4 years with an ICD in place for an average of 4.9 years (range 0.15-20.1) with age at implant ranging from 14.6 to 73.8 years old. In the study, 54% of patients received the implant for secondary prevention reasons. Testing instruments focused on anxiety (Florida Shock Anxiety Scale), device acceptance (Florida Patient Acceptance Survey), functional capacity (Duke Activity Status Index), and depression and anxiety (HADS).

Results showed increased anxiety and poorer functioning in the younger age cohort (designated in the study as younger than 35 years old). Younger age, poorer functional capacity, high frequency of ICD shock, and shorter time since ICD implant predicted anxiety and general psychological distress. Anxiety and device acceptance was not associated with sex or family history. The authors concluded that anxiety levels tend to be higher in the ARVC population because there is a larger proportion of young patients with potentially bad shock histories; however, the genetic etiology of the disease itself may play a role. The specific genetics were not discussed, however, approximately half of the patients had a confirmed desmosomal mutation. Although the majority of individuals with ARVC who had an ICD in this study did not appear to have

presented with clinically significant anxiety or depression, a significant minority may have poorer adjustment.

A study by Webster et al. (2014) also explored the psychiatric functioning of children and adolescents with cardiac rhythm devices (52 ICD, 114 pacemakers), and found an increased prevalence of psychiatric disorder in this population. Notably, these were heterogenous cardiac disorders and not specifically ARVC.

ICDs in ARVC: posttraumatic stress disorder

The only study found in relation to PTSD in the ARVC population was done by Ingles et al. (2013). Ingles et al. analyzed psychological well-being and posttraumatic stress associated with ICD treatment in young adults with a clinical diagnosis of genetic heart disease (inherited cardiomyopathy or primary arrhythmogenic disorder) from the Australian Genetic Heart Disease Registry. Of note, the largest cohort of participants had hypertrophic cardiomyopathy, not arrhythmogenic disorder (because HCM is the most common genetic cardiomyopathy). Patients had to have an ICD for at least 12 months. The mean age was 45 years old. 81% of participants had ICD for primary prevention. Participants underwent psychological evaluation using the HADS and the IES-R. Scale scores were found to be within the normal range for all groups, but analysis of certain subgroups showed excess difficulties, with scores higher than general population averages. Using univariate linear regression, it was found that female sex, a history of

syncope, presence of other comorbid medical conditions, and those reporting events related to ICD device complications were indicative of increased depressive, anxiety and posttraumatic stress symptoms (represented by scores on the HADS and the IES-R). Another subgroup, patients who reported ICD shocks, had higher posttraumatic stress test scores. These participants were more likely to be female, and had a longer time to first shock. All of these findings were statistically significant.

Effects of the ICD and ARVC in family members of ARVC patients

Adjustment to life with an ICD may be challenging for patients, their partners, and other family members, with disease types and individual characteristics likely influencing the process. Symptoms of anxiety and depression, fears of death and losing a partner, fear of device malfunction, and major changes in the family dynamic can all influence family life. Studies show that families of patients with ICDs can be as strongly affected by psychological sequelae as patients themselves (Ladwig et al., 2008; Van den Broek et al., 2013). Etchegary et al. (2016) explored the economic burden associated specifically with the *TMEM43* p.S358L inherited genetic cardiac condition in families. Several perceived economic burdens were identified, highlighting one of many ways that life with ARVC and an ICD can be challenging for family members. Etchegary et al. (2017) also did a qualitative study that explored the emotional, relationship and social impacts in carriers and their family members. Many factors caused distress for ICD patients and their family members, including (but not limited to) awareness of the ICD in the chest,

discussion of family history with potential partners, and stress related to the inability to participate in certain strenuous activities (Etchegary et al., 2017). In this sense, ICD implantation can be seen as a dyadic issue affecting both the patient and their partners and family members (Rottmann, Skov, Andersen, Theuns, & Pedersen, 2018). Emotional distress in partners may thus influence the patient's wellbeing, but is also a burden on its own for the partners, and therefore needs to be further explored.

There is scarce literature related to this topic. Some studies report that up to 30% of ICD patients suffer from anxiety and depression. Partners report equal levels of depression and sometimes even higher levels of anxiety as the patients themselves (Rottmann et al., 2018).

Rottmann et al. (2018) examined whether perceived social support and clinical patient characteristics are associated with change in couples' symptoms of anxiety and depression in the first year after ICD implantation, and explored whether this differed between patients and partners. This was a prospective cohort study, comprised of 286 participants in the Netherlands, with a mix of patients and their partners. Patients had received the ICD for primary and secondary prevention, were predominantly males (80%), with a mean age of 59 years, and the majority had coronary artery disease. A smaller proportion (31%) also had symptomatic heart failure. Symptoms were measured using the HADS for anxiety and depression, and the Multidimensional Scale of Perceived Social Support (MSPSS). The results showed that higher perceived social support prior to ICD implantation was associated with greater reductions in anxiety and depression for all parties

involved. In patients who received an ICD shock, or who received the ICD for secondary prevention purposes, higher levels of depression and anxiety were found in the patients themselves, and in their partners. The associations applied to both patients and their partners equally. Perceived social support was highly correlated with symptoms of anxiety and depression and predicted changes in psychological distress.

Ladwig et al. (2008) investigated QOL in patients with ICDs after the first year of implantation and found that high rates of shock increased the anxiety of both the ICD patients and their partners and worsened QOL for both.

Redhead et al. (2010) also explored the prevalence of anxiety and depression in ICD patients' partners, whom had experienced shocks and shock storms. Shock discharges from the ICD device increased levels of anxiety and depression in the patient and their spouse, well above normative population levels.

Van den Broek et al. (2013) also found positive correlations between distress in ICD patients and distress in their partners, with regards to depression and anxiety symptoms ($r= 0.19\text{-}0.43$, $P's<0.001$). Generally, partners experienced more anxiety and patients more depression.

Pedersen et al. (2009) reported that partners had significantly higher levels of anxiety compared to patients, but not depressive symptoms. This study used the same study sample as that of

Rottmann et al. (2018) (described above). Partners were predominantly female, while patients were predominantly male. Symptoms were measured using the HADS and were found to be worse at baseline, with gradual improvement over time after ICD implantation (follow up at 6 months). Partners of patients with a secondary indication for the ICD had higher anxiety and depressive scores compared to partners of patients with primary indications for the ICD. No other statistically significant associations were found. Only participants with no prior diagnosis of mental illness were included in the study. The results remained significant after adjusting for potential confounders and there was no difference between sexes noted.

Overall summary

ARVC is a genetic disorder with multiple genetic subtypes and an extremely variable clinical course. The genetics are mendelian, but have a complexity of phenotypic expressivity and presentation. Many variants of ARVC have been identified to date. A lethal subtype of ARVC, caused by a p.S358L mutation in the *TMEM43* gene is seen in the Province of NL, Canada. This subtype of ARVC is fully penetrant and often presents with SCD. This patient cohort has been followed since 1998 by the Health Sciences Cardiology Department in St John's, NL. An ICD for primary prevention purposes is the treatment of choice in this population given the high risk of SCD.

The ICD has been proven to save lives. Recent literature suggests ICD therapy is indicated in

high-risk individuals. However, little is known about the psychiatric sequelae and mental health burden of such devices. Concerns regarding QOL, depression, anxiety, and posttraumatic stress have been identified in patients with ICDs. However, there is scant literature with regards to the effects of the ICD on mental health sequelae in ARVC patient cohorts specifically. Additionally, there is no quantitative information available in the *TMEM43* patient cohort in NL. The few manuscripts addressing the issue show evidence of similar mental health concerns as those with ICDs for other indications. In our study we will explore the above-mentioned associations in the homogenous *TMEM43* p.S358L patient cohort.

Symptoms of anxiety, depression, and posttraumatic stress may be underrecognized in the ICD patient population, as well as in close family members, and the research done thus far [highlighted above] illustrate the concerns regarding mental health sequelae in these populations. It is thus crucial to analyze this phenomenon further to provide data which may help determine avenues for appropriate management.

Patients with ICDs provide the opportunity to more closely link mental health sequelae and the impact of the ICD on emotional health. In the *TMEM43* p.S358L patient population in particular, considering the disease follows a more malignant course as compared to other ARVC subtypes, ICD implantation surely prevents early death. However, each shock of the ICD device can cause severe stress on the individual, whether it be the realization of their mortality, or the burden of the genetics of the disease on the family, causing undue stress on young individuals and their

families. ICD implantation is not a trivial procedure, and the decision to pursue such therapy is a complex one. As a result, concerns over mental health sequelae are an important consideration in this population. No study has assessed in a robust manner the effect of the ICD on a patient population where the ICD clearly saves lives (and has allowed up to 30 extra years of life based on our latest data), where the etiology is a single gene mutation, and where individuals born at the same *a priori 50%* risk of the mutation but shown to be unaffected (negative siblings) can be assessed (Hodgkinson et al., 2016).

Therefore, this research project will focus on identifying symptoms of mental illness (specifically anxiety, depression, and posttraumatic stress symptoms) in this population treated with an ICD and assess whether these relate to severity of the disease in various forms. A secondary assessment will compare prevalences to the general population. Additional analysis will compare prevalences to unaffected family members of this patient cohort (negative siblings who were born with the same pedigree risk but shown to be negative, and unrelated spouses of those with an ICD) in hopes of understanding prevalence, correlations and potential causes more clearly.

This thesis will focus specifically on the ARVC mutation positive group with an ICD. There are two other arms of the overall study: the first is focusing on the negative mutation sibling group; the third group focuses on the genetically unaffected, unrelated spouses group. Each respective project will explore symptoms of depression, anxiety, and posttraumatic stress in each of these groups as they relate to the severity of disease in their sibling or partner, and compare these with

general population norms. Each project ends with a brief comparison of the mental health parameters between the groups.

Research Question and Objectives

Our research project seeks to identify symptoms of depression, anxiety, and posttraumatic stress in the large founder population in NL, Canada where ARVC, causing early SCD is caused by a genetic mutation (p.S358L) in a gene called *TMEM43.* We wish to assess three separate groups within the large family population: (a) Persons with the p.S358L mutation, who have been provided with an ICD for prevention of SCD, (b) siblings of those persons with an ICD who were born at an *a priori 50%* risk of having the genetic disease causing mutation (p.S358L in *TMEM43*) who were shown not to have the mutation and thus were deemed free of the disease and (c) the unaffected, non biologically related spouses of those with an ICD.

Given the lifelong impact of the ICD, qualitative evidence of our team, and anecdotal evidence we have from our patient clinics, we feel it is vital to explore the psychological ramifications associated with having this *TMEM43* mutation and the treatment used to offset early death. We wanted to obtain data which will either support (or not) the need for our clinics to provide mental health support alongside cardiac care. We expect mutation positive ICD recipients to score higher on these scales than their unaffected siblings and biologically unrelated spouses, but expect all groups to score higher than population norms.

The primary objectives of the current study are the following: to determine the prevalence of depression, anxiety, and posttraumatic stress symptoms in the ICD group, including how it compares to general population norms; and to determine whether the severity of psychiatric symptoms correlates with severity of disease in the ICD group (represented by a variety of demographic and clinical variables). Additional analyses will include comparisons of psychiatric symptom prevalences among the three groups (ICD group; mutation negative siblings group; un affected spouses). The data obtained from the study may alter the provision and type of health care in this patient cohort regarding their mental health.

CHAPTER 3: METHODS

Study population/participants

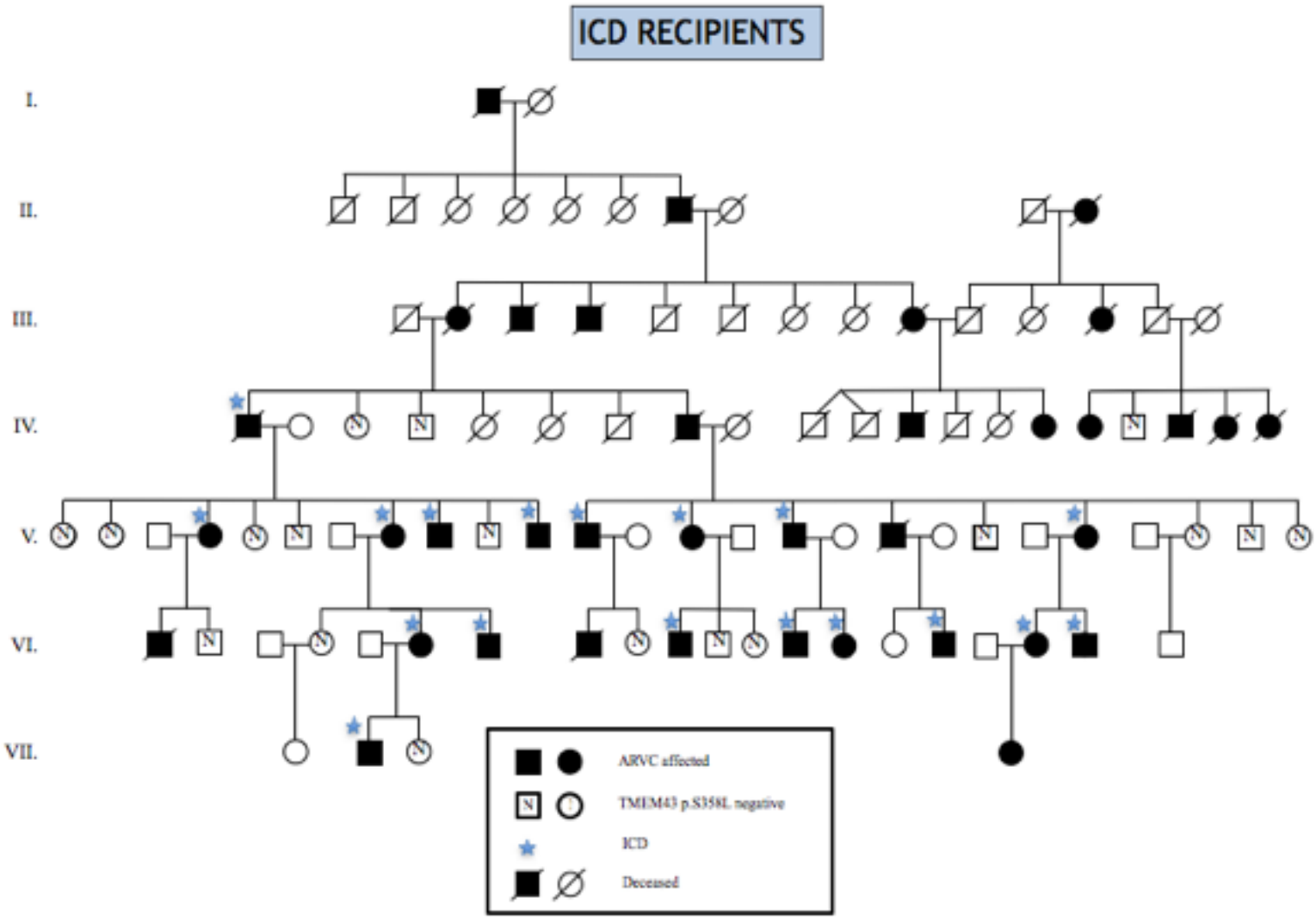

Figure 3.1: TMEM43 p.S358L pedigree, highlighting mutation positive ICD recipients

This retrospective observational cohort study focuses on NL ARVC families with the *TMEM43* p.S358L mutation. There are currently 27 families (new families continue to be ascertained) with

this condition, the largest of which covers 10 generations and comprises approximately 1200 individuals in the extended family tree. To be eligible for this study, participants had to have a verified diagnosis of ARVC with a known *TMEM43* p.S358L mutation, an ICD, and currently be managed by a cardiologist through the ICD clinic at the cardiology department situated in the Health Sciences Centre in St. John's, NL. ARVC ICD patients are usually assessed every six months. Cardiology staff who follow this unique patient population include Drs. Connors and Paulin, with several nurses and ICD specialists. The ARVC population is a subset of the patients seen at the clinic, the majority of whom are ICD recipients following a myocardial infarction.

This project involved three groups of participants. The responsibility for the collection of data and analysis for each group was taken by a different M.Sc student.

1. p.S358L *TMEM43* positive ICD recipients, n=106 (Dr. Magda Orzylowski)
2. Mutation negative siblings of ICD recipients, n=146 (Ms. Natalie Butt)
3. Mutation negative spouses of ICD recipients, n=63 (Ms. Mary Walsh)

Quantitative data analysis for each group was solely undertaken by each respective student, with the same survey tools used for each of the 3 groups (PHQ-9, SAS, PCL-C). Results of the survey instruments were shared among the 3 research projects, only to compare scale scores and proportions among the 3 groups, and for discussion purposes.

We were constrained in this study by the finite number in each group based upon the currently

ascertained families. Therefore, this was a sample of convenience. The experimental group comprised the ICD recipients, and the control groups comprised their mutation negative siblings and their unrelated spouses.

Survey instruments

Studies in the area of ICD and mental health, especially in ARVC, are scarce. A variety of scales and questionnaires are available for use for any research addressing psychiatric sequelae, mental health burden, and QOL. Some scales focus on hospitalized patients, while others assess specific shock burden. Few studies have looked at the general mental health burden in this type of patient population which require testing instruments that are broad, generalized, and applicable to the general population as well as the study sample.

The objective of our study was to assess three specific areas of mental health: symptoms of depression, anxiety, and posttraumatic stress. There are various scales that can help aid in the diagnosis of these disorders, but a full clinical interview with a health care professional is required to fully diagnose an individual. However, various scales can reliably identify symptoms.

Individuals were asked to complete three short, validated, questionnaires. The testing instruments for our study were chosen for several reasons. First, we wanted scales that were easily accessible, brief and generalizable. Specific mental health scales for cardiac patients and those with chronic

illness have been widely used and supported by past and current literature. Examples include the Patient Health Questionnaire-2 and 9 (PHQ-2, PHQ-9) (Tomitaka et al., 2018; Tomitaka et al., 2018; Stafford, Berk, & Jackson, 2007; Wang et al., 2015), the Hospital Anxiety and Depression scale (HADS), and Beck Depression inventory (BDI) (Ceccarini, Manzoni, & Castelnuovo, 2014; Haddad et al., 2013). A newer version of the PCL, the PCL-S, has also been validated in populations with acute coronary syndrome (Sumner et al., 2015). However, these scales are more commonly used in the hospital setting. In addition, there have been no scales validated specifically for inherited cardiac disease patients. Second, the scales had to be easy to complete and easy to interpret since they were self-rated. Third, the scales had to be valid and reliable. And finally, the scales required a broad focus on symptoms of depression, anxiety, and posttraumatic stress, rather than identification of specific disorders, thus ensuring that a broader range of mental health sequelae were captured.

The scale instruments we chose for our study are listed below:

1) The Patient Health Questionnaire (PHQ-9) (APPENDIX C)

(Kroenke, Spitzer, & Williams, 2001)

2) The Zung Self Rating Anxiety Scale (SAS) (APPENDIX C) (Zung, 1971)

3) The PTSD Checklist for Civilians (PCL-C) (APPENDIX C)

(US Department of Veteran Affairs, 2012)

Depression instrument

We used the Patient Health Questionnaire-9 (PHQ-9). This is a 9 item self-administered 4 point Likert scale that asks questions related to symptoms of depression as per DSM5 criteria. Question topics include mood, sleep, engagement, energy, appetite, self-esteem, concentration, and suicidality. The PHQ-9 has been extensively studied (Kroenke, Spitzer, & Williams, 2001; Tomitaka et al., 2018; Hammash et al., 2013) and is especially useful in diagnosing depression, as well as assessing severity in medical illness, because it includes symptom assessment and functional impairment questions (Ramasubbu et al., 2012).

A score ≥10 points corresponds to evidence of moderate depression. This cut off threshold corresponds to 88% sensitivity and specificity in a heterogenous primary care population (Kroenke, Spitzer, & Williams, 2001).

Anxiety instrument

Symptoms of anxiety were measured using the Zung self-rated anxiety scale (SAS). This is a self-rated, 20-question assessment scale that measures anxiety levels based on scoring in four groups of manifestations: cognitive, autonomic, motor and central nervous system symptoms. Questions are answered based on a Likert scale of 1-4: (1) a little of the time; (2) some of the time; (3) good part of the time; (4) and most of the time. Questions encompass a broad range of

anxiety related topics, with aspects of several DSM5 anxiety disorders, but mostly encompassing generalized anxiety and panic symptoms.

The total raw score ranges from 20-80 points. The raw score then needs to be converted to an 'index' score using a conversion chart provided with the testing instrument (see APPENDIX C). A raw score of 20 corresponds to an index score of 25; a raw score of 80 corresponds to an index score of 100. A final index score of ≥45 points corresponds to mild to moderate anxiety levels. This was based on the following breakdown of the index scale measures: < 45 points= normal range; 45-59 points= minimal to moderate anxiety; 60-74 points= marked to severe anxiety; and ≥ 75 points= most extreme anxiety (Dunston & Scott, 2018). The data related to these cut points included clinical and community populations, mostly comprising undergraduate university students.

Post-traumatic stress instrument

Symptoms of posttraumatic stress were measured with the post traumatic Checklist- civilian version, (PCL-C). This is a 17 item, self-administered rating scale pertaining to a DSM5 diagnosis of posttraumatic stress disorder and includes questions related to key symptom areas of intrusion, hyperarousal, avoidance, as well as cognitive and mood changes. Respondents indicate how much they have been bothered by a symptom over the past month using a 5-point Likert scale, ranging from (1) not at all to (5) extremely. Two versions of the scale exist which relate to any

traumatic event: a military version and a civilian version, the latter used in this study.

The cut off values for the PCL-C scale were more complex as compared to the other two scales. Intended for civilian use in the general population, the PCL-C scale was edited from the original PCL scale designated for military personnel. It is important to note that the gold standard for diagnosing PTSD is a structured clinical interview. The PCL-C can only be scored to provide a presumptive diagnosis. A combination of symptom patterns consistent with DSM-IV criteria and reaching a specific severity threshold are both necessary for an appropriate diagnosis. The interpretation of the scores on the scale are dependent on the clinical population one is working with and the goal of the assessment. When informing potential diagnosis of PTSD, or to minimize false positives, a higher cut point is considered. The prevalence of PTSD in the target setting must also be considered. Generally, the lower the prevalence of PTSD in a given setting, the lower the optimal cut point. In settings with expected high rates of PTSD (such as medical health clinics) it is advised to consider a higher cut point. Guidance and suggested cut-point scores are provided for the PCL-C through the National Center for PTSD (U.S. Department of Veteran Affairs, 2012; Blanchard, Jones-Alexander, Buckley, & Forneris, 1996; Wilkins, Lang & Norman, 2011).

The ICD clinic would be considered a specialized medical (cardiac) clinic. In addition, this is a clinical setting where we would expect higher rates of PTSD given the impact of the ICD device and from previous evidence in the literature. Although there is no specific literature regarding

posttraumatic stress symptoms in our unique population, previous literature review has given PTSD prevalence estimates ranging between 21-31% in ARVC ICD populations (Kapa et al., 2010; Ingles, Sarina, Kasparian, & Semsarian, 2013; Ladwig et al., 2008; Thylen et al., 2016; Rahmawati et al., 2013). Therefore, the most appropriate cut point in our *TMEM43* p.S358L mutation positive ARVC ICD population would be 36 points (corresponds to an estimated PTSD prevalence of 16-39%).

Recruitment

The *TMEM43* p.S358L population is closely followed by Memorial University and the Health Sciences Centre. The ICD recipients (n=106) were originally recruited as part of the SCD research project: HREB 00-176, and their diagnosis and management has been a close collaboration between the clinical and the research SCD teams. Participants for this study were recruited from the Health Sciences Cardiology ICD clinic or via telephone call by a research team member within the circle of patient care. All ICD subjects are seen at the ICD clinic at the Health Sciences Centre in St. John's, Newfoundland every six months for follow up for their ICD. The cardiologist responsible for each *TMEM43* p.S358L ICD recipient asked if they were willing to hear about the research project from a research team member. This required a team member to attend each of the outpatient clinics in which an ICD patient was identified for an appointment. Outpatient clinics occurred on Monday and Thursday afternoons and recruitment occurred between November 2017 and July 2019.

Considering the finite potential participant pool for this study, there were limited inclusion and exclusion criteria. For the 3 separate groups of participants (ICD group; mutation negative siblings; unaffected spouses). Participant recruitment focused on ICD clinic and telephone recruitment, with geographical distribution having an effect on potential participants. Those living more locally, or easily accessible by telephone, made up the largest proportion of participants. Individuals who did not complete all 3 questionnaires were excluded from further analysis. For ICD patient participation, individuals had to have a confirmed TMEM43 p.358L mutation with an ICD (affected or unknown statuses were excluded as they did not have confirmation of genetic mutation).

If participants agreed to hear about the study, they spoke with the research team member who described the project and obtained consent. Patients could choose to complete the questionnaire package immediately in the clinic, or were given the option to take the packages home and mail it in at a later time for which prepaid envelopes were provided. The time taken for completion of the questionnaires was considered to be on average 15 minutes.

If unaffected siblings and/or spouses of ICD participants accompanied the ICD patient to clinic, they would be approached regarding recruitment at the same time as the ICD subject. Otherwise, they were contacted by phone by Dr. Hodgkinson (who has a relationship with the families covering two decades) and mailed the consent form and the questionnaire package (following verbal consent to do so). For recruitment of the mutation negative siblings group and the unaffected

spouses group over telephone, contact was initiated by one of the team members. This included the genetic counselor working with the families over several years. The choice of individual to make the call was determined by which individual had most prior contact. If the individual was interested, a research package was sent to them by mail.

Research Objectives

Primary

1. To determine the prevalence of anxiety, depression, and posttraumatic stress symptoms in ICD recipients.
2. To determine whether the severity of psychiatric symptoms correlates with severity of disease in ICD recipients (e.g., type and number of discharges from the ICD/ other cardiac morbidities: collected and maintained in a large dataset under the cardiomyopathy project HREB 00-176).
3. To obtain data which might inform the provision and type of health care in this patient cohort regarding their mental health.

Secondary

1. To utilize the prevalence of depression, anxiety, and posttraumatic stress symptoms in the unaffected siblings, and spouses of ICD recipients (M.Sc theses by Mary Walsh and Natalie Butt 2020, available through the MUN health sciences library) and to compare the

prevalence of depression, anxiety, and posttraumatic stress symptoms between all three groups.

2. To compare the prevalence of depression, anxiety and posttraumatic stress symptoms in ICD recipients with general population levels.

Follow up calls (reminders)

The research team was available for contact if necessary throughout the study. If a questionnaire package had not been received four weeks following initial contact (where the participant tentatively agreed to participate) one follow up call was made. No further calls were made after this point.

Mental health concerns

After packages were returned, the PI and/or supervisor contacted participants for follow up if deemed necessary. Reasons for follow up calls included clarification of scale information, and mental health follow up as deemed appropriate based on scale scores. Participants who had very high scores on the questionnaires were followed up by the supervisor and/or supervising psychiatric resident and reviewed with the psychiatrist appropriately and in a timely manner, as per

original protocol guidelines. This included appropriate contact information for the research team, as well as timely medical follow up where deemed necessary.

Data collection

Research Package

The research package included the following: the cover letter and consent form explaining the study (APPENDIX B), and the three validated mental health measures as follows: (a) The Patient Health Questionnaire (PHQ-9) (b) the Zung self-rating anxiety scale (SAS) and (c) the PTSD checklist (PCL-C) (APPENDIX C).

Participants' names were not associated with their responses. The ID number from their previous association with the wider research project (HREB 00-176) was used as a de-identified measure associated with all scales sent to individuals or completed at the clinic.

Secondary data from ARVC *TMEM43* dataset

A dataset was created in 1998 as a means of collecting information on families with a severe cause of SCD, later determined to be ARVC due to *TMEM43* p.S358L. This effort was undertaken to have readily accessible data on this population to (a) find the causative gene, (b) determine the natural history of the condition, and (c) to determine the clinical course of disease following treatment (primarily to determine the efficacy of treatment). Individuals in the dataset are those born at an *a priori 50%* risk of inheriting ARVC, thus comprising affected individuals (criteria to determine affected and unaffected status criteria for this population can be found on page 31),

individuals born at 50% risk but shown to not have the disease, and those remaining at 50% risk. The dataset contains over 1500 variables for each individual, which includes demographics, diagnostic procedures, clinical results, pharmaceutical and non-pharmaceutical treatments, cardiac interventions, cardiac events, hospital and clinic visits, and clinician notes. The ICD cohort and their siblings are therefore all consented participants in this large cardiomyopathy/SCD study (HREB 00-176).

For the purposes of our study, consented individuals' scale scores and relevant variables from the secondary dataset were moved to a separate dataset for analysis identifiable only by study number, and no other identifying variables (such as date of birth or provincial health card number) were included. The dataset was used to link anonymous surveys to the ID participant (the ICD patient and unaffected siblings as applicable).

There is no information on the biologically unrelated spouses in the dataset. Information on spouses was added to this study dataset. The severity of disease data for the spouses was that of their spouse with an ICD.

Variable information was extracted from the main dataset including patient demographics such as age and sex, ARVC clinical status, whether they had seriously affected 1st degree relatives (those with SCD, an ICD or a cardiac transplant), method of diagnosis, and sex of transmitting parent. Clinical information included genetic mutation status, heart transplant status, number of

hospitalizations, number of appropriate and inappropriate shocks, age at ICD implantation, and whether they experienced presyncope/syncope and/or palpitations. There were approximately 1500 variables in this registry, a very comprehensive database. For the purpose of our study, variables were chosen based on completeness (≥80%), relevance to the study objectives (possible clinical relevance to psychiatric sequelae and ARVC disease severity), and evidence from literature review, as well as clinical experience with the population.

The variables abstracted from the main dataset for use in this study are listed in Table 3.1.

Table 3.1: ICD patients' clinical and demographic variables

ICD patient variables	Demographic	Clinical
	Age	Method of Diagnosis
	First degree relative with SCD, ICD or heart transplant	Presyncope and/or syncope and/or palpitations
	Sex of transmitting parent	Heart transplant status
	Age at ICD implantation	Number of hospitalizations
		Number of appropriate shocks
		Number of inappropriate shocks

Data management

Data from the screening scales were entered into a de-identified copy of the ARVC *TMEM43* dataset containing a reduced number of variables (see Table 3.1 above) and analyzed using SPSS

statistical software version 22. Items on each mental health measure were summed as indicated on scale scoring guides to create an overall scale score for each participant.

Statistical analysis

Our sample population was a sample of convenience, therefore calculating a sample size would not affect our recruitment. However, with a potential participant pool of 92 *TMEM43* p.S358L ARVC ICD patients, a 5% margin of error, and a 95% confidence interval, would reveal a sample size of 75 participants; therefore slightly higher than our recruitment numbers yielded.

Survey response rates were calculated based on the number of respondents who provided consent and completed the surveys either in person or via mail. Incomplete packages were excluded. Packages returned with 1 or more scales not fully answered were considered incomplete. For the ICD recipients, 53 participants completed the surveys out of a possible 82 (65%). Descriptive statistics and frequencies were calculated to determine the demographics of the study population. For descriptive statistics this included mean, range, minimum, maximum, standard error, standard deviation, skewness, and kurtosis of each continuous variable, and mean and percentage were calculated for each categorical variable included. Detailed characteristics of the sample are discussed in the results section.

A flowchart (located at the beginning of the results section of the thesis, page 71) provided an outline of the recruitment process of participants and final participation numbers. Further specific details pertaining to recruitment are provided for the ICD group in the flowchart.

Using SPSS version 22 statistical software, continuous and categorical variables were analyzed using independent chi-squared tests and t-tests where appropriate. This included analyzing significant differences between scale scores among the 3 groups (ICD patients; mutation negative siblings; unaffected spouses) Scales were assessed according to published guidelines. Differences in outcomes were explored using linear models where appropriate. A P value of <0.05 was considered significant. A P value of <0.01 was considered if independent variables were highly correlated to one another ($B>0.7$).

Empirical analysis

Descriptive statistics and frequencies for continuous and categorical variables [demographic and clinical] were analyzed in the ICD group. This included a breakdown of mean scale scores, ranges and proportions of the scale scores. Certain variables were also analyzed by status (each of the three groups) and by sex.

Linear regression was used to determine associations between depressive, anxiety, and posttraumatic stress symptoms. Univariate analysis using Pearson product-moment correlation coefficient and Spearman correlation coefficient were conducted to analyze potential associations to the dependent variables of PHQ-9, SAS, and PCL-C scale scores. Variables chosen for univariate analysis were based on their potential effect on ARVC disease severity. This included previous literature review that may have identified potential demographic or clinical variables (if applicable) involved in increased severity of ARVC disease, or variables that had potential correlation to

psychiatric sequelae. Statistically significant correlations were analyzed using multivariate analysis. Multiple linear regression analysis was used for each of the three scales: PHQ-9, SAS, and PCL-C.

The scale scores were compared among the three groups (ICD recipients; mutation negative siblings; unaffected spouses). Mean scale scores and prevalences were compared among the groups using One-way between-group analysis of variance (ANOVA) and Fisher's exact test, respectively.

Proportions of positive symptomatology of depression, anxiety, and posttraumatic stress were compared to general population norms for major depressive episode/major depressive disorder, generalized anxiety disorder, and posttraumatic stress disorder in the ICD group. A sample test of proportions based on binomial distribution were used to compare scale proportions to general population averages provided in the Statistics Canada information database.

Data merger and storage

The data collected will be added to the larger dataset from this population started in 1998 (HREB 00-176) that has long been approved by the HREB. The data collected will be kept as a part of this larger dataset. Data will be stored on Dr. Hodgkinson's computer which is password protected and behind locked doors. Participants will be identified by a pre-existing ID number that is

the link to a genetic pedigree. No other identifiers will be retained for this study. All participants have an ID number from their previous association with the wider research project (HREB 00-176).

Hard copies of the consent forms and returned packages/scales were stored separately in a locked filing cabinet in a secure office at the Health Sciences Centre campus of Memorial University of Newfoundland.

Ethics

Ethics approval

This study was approved by the Health Research Ethics board under Application for General Research at Memorial University of Newfoundland under reference number HREB#20171983. Full board approval was granted on May 11, 2017 (APPENDIX A).

Ethical considerations

Specific ethical situations occurred that were related to certain respondents obtaining high scores on the scales. The participants knew that if they had high scores, they would be followed up. This was part of the study. Dr. Hodgkinson contacted these respondents initially and respondents agreed for further contact from Dr. Orzylowski (the psychiatry resident), Dr. Walsh (psychiatrist), Dr. Bassett, or their GP to discuss concerns further. On occasion, these persons were contacted by the cardiologists from the ICD clinic following high scores. Mental health resources were discussed and guidance was given as appropriate.

CHAPTER 4: RESULTS

Participants

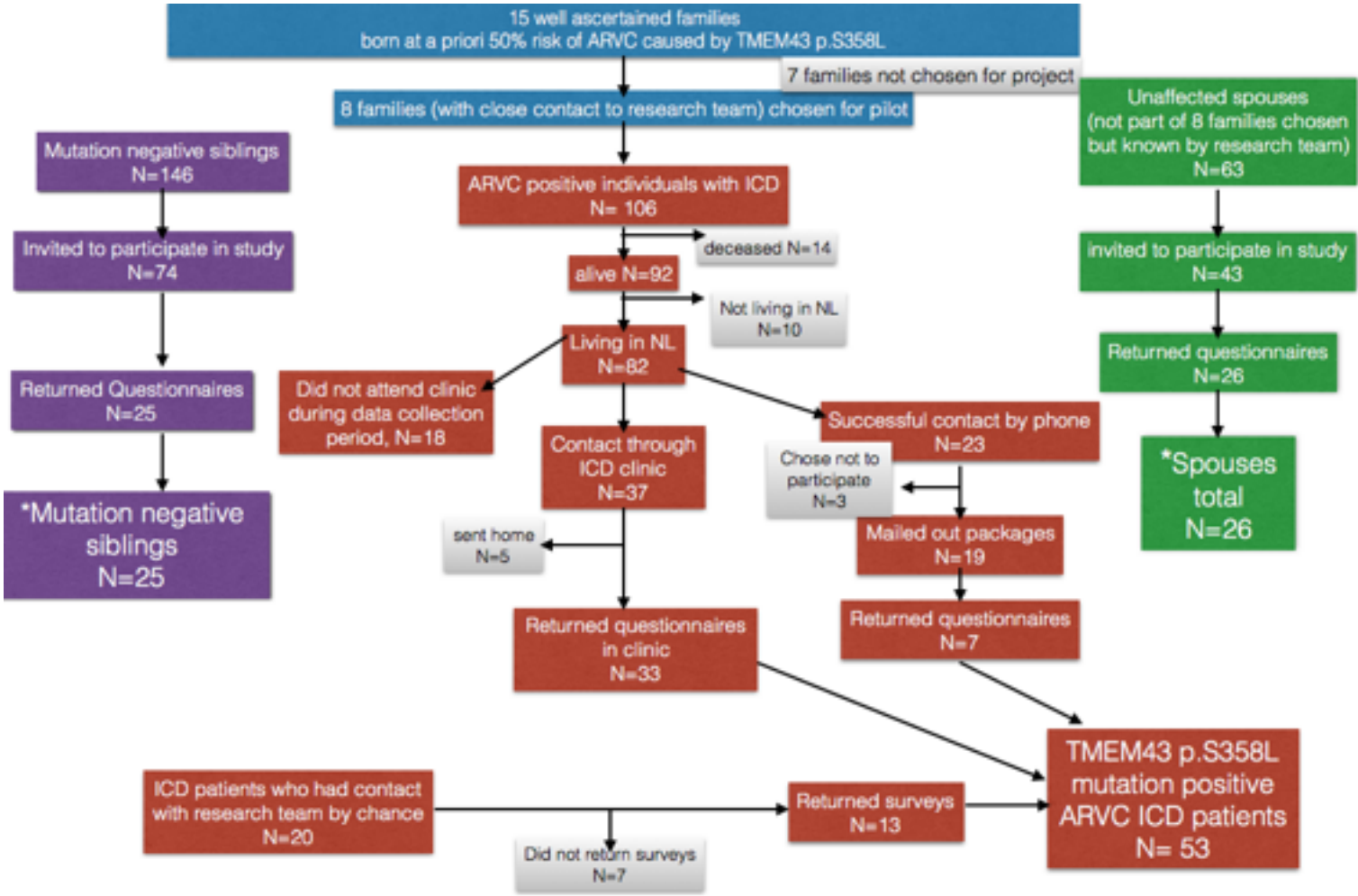

Figure 4.1: Recruitment of participants and final participation numbers

*refer to separate M.Sc thesis by Natalie Butt for further information regarding recruitment

** refer to separate M.Sc thesis by Mary Walsh for further information regarding recruitment

As per Figure 4.1 above, potential participants for the study comprised a total of 315 individuals (106 ICD patients, 146 mutation negative siblings, and 63 unaffected spouses).

The current analysis was part of a three-armed study, in which mutation negative siblings, and unaffected spouses were considered the control groups, while the ICD group was considered the experimental group. The majority of ICD patients were contacted directly through the ICD clinic. Where possible, mutation negative siblings and spouses were contacted through the clinic as well, but most were contacted via phone, with resulting lower contact retention levels.

In total, 197 participants (81 ICD+ 74 mutation negative siblings + 43 spouses) were successfully contacted and invited to take part in the study. 104 ultimately returned study questionnaires and comprised the overall study sample: 53 *TMEM43* p.S358L mutation positive individuals with an ICD device, 25 unaffected siblings born at *a priori 50%* risk of ARVC caused by *TMEM43* p.S358L, and 26 unaffected, biologically unrelated spouses.

The initial total sample of ARVC positive individuals with an ICD collected from the eight families was 106. These individuals were (or had at some time been) regularly followed by the ICD clinic at the Health Sciences Centre in St. John's, Newfoundland. Of the 106 potential recruits, 14 were now deceased, and ten no longer lived in Newfoundland and therefore no longer followed up at the ICD clinic. However, we were still able to contact some individuals who lived

outside of the province. This revised the potential ICD group number to 82 individuals. Therefore, from a potential 92 participants in the ICD group who could partake in the study (that were alive), 53 individuals participated. Eighteen individuals did not attend clinic during the data collection period. Four individuals were also missed in clinic. Thirty-seven individuals were contacted through the ICD clinic directly, with 33 returning survey packages in person at the clinic after completion. In addition, 20 individuals who were not part of the first eight families were contacted by chance through the ICD clinic as well, usually due to a person attending clinic unexpectedly, with 13 returning the survey packages. ICD patients who were not contacted through the clinic were contacted by phone (n=23) and 19 packages were sent via post following telephone recruitment. Seven of these individuals returned surveys. Therefore, a total of 53 survey packages were returned (Figure 4.1).

The ICD group cohort represented the largest group in the bigger three-arm study, representing 51% of the total sample and with a response rate of 53/82 (65%). This cohort is the focus of the current study and the analyses to follow.

The ICD group comprised 18 males and 35 females. The mean age of the group was 48.49 years old, with a wide age distribution between 22 and 71 years old. Demographic information is presented in Table 4.1.

Table 4.1: Demographic information on ICD cohort

Demographics	ICD cohort
N	53
% of total group	51
M:F counts	18:35
age, mean (standard deviation)	48.49 (1.422)
age (range)	22-71
20-29 year olds	8 (15.1%)
30-39 year olds	3 (5.7%)
40-49 year olds	16 (30.2%)
50-59 year olds	11 (20.8%)
60-69 year olds	13 (24.5%)
70-79 year olds	2 (3.8%)

Demographic and clinical variables examined in the ICD group are listed in the methods section in Table 3.1. Characteristics of these variables are listed in Table 4.2, stratified by sex. Considering males have a more malignant course of disease in this particular subtype of ARVC, describing the clinical features for ICD patients as a group, and subsequently by sex, can help identify any pertinent differences between the groups.

Table 4.2: Demographic and clinical characteristics of the ICD group

	Total ICD group	Males	Females
N	53	18	35
% of ICD total	100	34	66
Mean age	48.49 (13.81)	40.5 (13.47)	52.6 (12.23)
Age range	22-71	23-69	22-71
Mean age at ICD implant	36.98 (11.80)	29.96 (11.34)	40.59 (10.44)
Age range at ICD implant	13-57	13-51	22-57
Total shocks (range)	0-101	0-101	0-51
Mean # of appropriate shocks	8.36 (19.51)	10.82 (26.57)	6.97 (14.45)
# of appropriate shocks (range)	0-101	0-101	0-51
Mean # of inappropriate shocks	1.64 (5.387)	1.24 (2.33)	1.87 (6.55)
# of inappropriate shocks (range)	0-35	0-9	0-35
Mean # of hospitalizations	1.25 (0.81)	1.56 (1.25)	1.09 (0.373)
# of hospitalizations (range)	1-6	1-6	1-3
# with heart transplant	3 (5.6%)	2	1
# with a first degree relative with SCD or heart transplant	24 (45%)	6	18
# diagnosed by DNA	38 (76%)	17	21
# with presyncope and/ or syncope and/or palpitations	32 (60%)	11	21
The mother as transmitting parent	32 (60%)	10	22

*Reminder that diagnosis could be made clinically following a significant cardiac event, or by being an obligate carrier by pedigree

Psychiatric sequelae in the study group

The prevalence describes how frequently a specific disease or a specific risk factor occurs in a population at a defined point in time. Table 4.3 presents the prevalence of depressive symptoms, anxiety symptoms, and posttraumatic stress symptoms in the ICD group.

Table 4.3: Prevalence of depressive, anxiety and posttraumatic stress symptoms in ICD group

	ICD group N=53	Scales legend
PHQ-9 mean	7.28 (6.41)	Mild depressive symptom range
PHQ-9 score range	0-29	0-29
PHQ-9 ≥10 points (%)	15/53 (28.3%)	Depressive symptoms (points) 0-4: minimal or none 5-9: mild 10-14: moderate 15-19: severe
SAS mean	43.66 (12.15)	Normal range
SAS score range	24-68	20-100
SAS ≥45 points (%)	26/53 (49%)	Anxiety symptoms (points) 20-44: normal range 45-59: mild to moderate 60-74: marked to severe ≥75: extreme anxiety
PCL-C mean	33.25 (12.87)	Moderate to high post traumatic stress symptom range
PCL-C score range	17-65	17-85
PCL-C ≥36 points (%)	17/53 (32%)	Posttraumatic stress (points) 17-29: little to no severity 28-29: some PTSD symptoms 30-44: moderate to moderately high severity of PTSD symptoms 45-85: high severity of PTSD symptoms

Legend:

Patient Health Questionnaire-9 (PHQ-9) depression score range: 0-4 minimal or none; 5-9 mild; 10-14 moderate; 15-19 moderately severe.

Zung Anxiety score range: 20-44 normal range; 45-59 mild to moderate anxiety levels; 60-74 marked to severe anxiety levels; ≥75 extreme anxiety levels.

Posttraumatic Stress Checklist- Civilian version (PCL-C) score range: 17-29 little to no severity; 28-29 some PTSD symptoms; 30-44 moderate to moderately high severity of PTSD symptoms; 45-85 high severity of PTSD symptoms.

Univariate analysis: Results from Pearson Correlation analysis of depression, anxiety, and posttraumatic stress symptomatology

A correlational analysis was undertaken to explore relationships among demographic and clinical variables and the three mental health scales. Pearson correlation coefficient analysis was used for variables following a normal distribution pattern, while Spearman's correlation coefficient analysis was used for non-normally distributed variables. Correlation analyses were performed with the continuous variables listed in Table 3.1 on page 66. Only variables significant at the $p<.05$ level were retained for further analyses. The results of the correlation analysis are presented in Table 4.4.

Table 4.4: Correlational analysis among study scales, clinical and demographic variables

Correlation Analysis r (p-value <0.05)	**PHQ-9 Depression Score (N=53)**	**Zung Anxiety Scale (N=53)**	**Posttraumatic Stress Scale (N=53)**
R (p<0.05)	R (p<0.05)	R (p<0.05)	R (p<0.05)
Age	-0.127	-0.134	**-0.322 (0.019)**
Gender	0.072	-0.012	0.023
Age at ICD implantation	-0.114	-0.100	-0.233
No. of Hospitalizations	0.051	0.265 (0.055)	0.199
No. of appropriate shocks	0.246	**0.335 (0.022)**	0.287 (0.051)
No. of inappropriate shocks	0.045	0.052	-0.003
Method of diagnosis	-0.080	-0.048	-0.066
First degree relatives with SCD or heart transplant	0.026	0.128	0.106
Presyncope and/or syncope and/or palpitations	-0.214	-0.093	-0.104
Sex of transmitting parent	0.086	0.014	0.049
Heart Transplant	0.147	-0.016	0.064
PHQ-9	1	**0.644 (0.000)**	**0.731 (0.000)**
SAS	**0.644 (0.000)**	1	**0.675 (0.000)**
PCL-C	**0.731 (0.000)**	**0.675 (0.000)**	1

Legend:
Significant correlation values are bolded in the table and highlighted. P values <0.05 are provided in brackets only for those variables statistically significant.

Pearson correlation coefficient (P): PHQ-9; SAS; PCL-C; Age; Age at ICD implantation

Spearman correlation coefficient (S): gender; Number of hospitalizations; Number of appropriate

shocks; Number of inappropriate shocks; method of diagnosis; first degree relatives with SCD or heart transplant; presyncope and/or syncope and/or palpitations; sex of transmitting parent; heart transplant status.

Several variables were correlated to the mental health scale scores. In addition, the scale scores were positively and significantly correlated to one another. For the PHQ-9 scale, statistically significant positive correlations were found only with the Zung Anxiety Scale and the PCL-C scale. For the Zung Anxiety Scale, significant associations were also found with the PHQ-9 scale and the PCL-C scale, but also with number of appropriate shocks (B=0.335, P= 0.022). A greater number of appropriate shocks from the ICD device were moderately positively associated with higher Zung anxiety scale scores in ICD patients. Number of hospitalizations was almost positively statistically significant as well (B= 0.265, P= 0.055).

For the PCL-C scale, significant associations were found with the PHQ-9 scale, the Zung anxiety scale, and age. Increased post-traumatic stress scale scores were again strongly associated with having high scores on both the PHQ-9 and the SAS. In contrast, age was negatively correlated with PCL-C scores, showing that a younger age was moderately correlated to having increased PCL-C scores (B=-0.322, P=0.019). Number of appropriate shocks was almost positively significantly associated as well (B=0.287, P=0.051).

Guided by the results of the correlational analysis, significant variables were entered into multiple regression models.

Results from Multiple linear regression analysis of the scale scores

Depression and variables of disease severity

Linear multiple regression analysis was performed with PHQ-9 scale scores as the dependent continuous variable, and the following continuous independent variables: Zung anxiety scale scores and PCL-C scale scores.

The Model Summary R squared value was 0.576 [adjusted R squared=0.559]. Therefore, roughly 56% of the variance in the dependent variable (PHQ-9 scores) was explained by the model. The ANOVA p-value of 0.000 indicated that our model reached statistical significance. Thus, participants scoring higher on the anxiety and posttraumatic stress scales were also likely to score high on the depression scale (Table 4.5).

Table 4.5: Effect of independent variables on PHQ-9 depression scale scores

	beta value interpretation	p-value	CI (95%)	Part correlations
SAS	0.277	0.031	[0.014-0.278]	0.042
PCL-C	0.544	0.000	[0.146-0.396]	0.162

The variable making the strongest unique contribution was the PCL-C score, when the variance explained by the SAS scores in the model were controlled for.

Anxiety and disease severity variables

Standard multiple regression analysis was performed with Zung anxiety scale scores as the dependent continuous variable and the following continuous independent variables: PHQ-9 scores, PCL-C scores, and appropriate numbers of shocks.

The Model Summary R squared value was 0.533 and the adjusted R squared was 0.501. Therefore, 50% of the variance in anxiety scores was explained by the model. The ANOVA p-value of 0.000 indicated that our model reached statistical significance. The regression analysis revealed that depression scale scores and posttraumatic scale scores were significantly, and positively, related to anxiety scores (Table 4.6). Higher levels of depression and posttraumatic stress as measured by study scales predicted higher anxiety scores.

Table 4.6: Effect of independent variables on Zung Anxiety scale scores

	Beta value interpretations	p-value	CI (95%)	Part correlations
PHQ-9	0.346	0.029	[0.070-1.243]	0.055
PCL-C	0.396	0.014	[0.079-0.669]	0.071
No. of appropriate shocks	0.174	0.108	[(-0.025)-0.241]	0.029

The variable making the strongest unique contribution was the PCL-C score, when the variance explained by all other variables in the model was controlled for. PHQ-9 also made a unique, statistically significant contribution.

Posttraumatic stress and disease severity variables

PHQ-9 scores, SAS scores, and age were variables chosen for the multiple regression analysis based on the correlational analysis.

The Model Summary R squared value was 0.650 [adjusted R squared=0.629]. Therefore, approximately 63% of the variance in the dependent variable (PCL-C scores) is explained by the model, with a p-value of 0.000, indicating that our model reached statistical significance. Unique contributions of each of the independent variables are outlined in Table 4.7.

Table 4.7: Effect of independent variables on PCL-C scale scores

	Beta value interpretations	p-value	CI (95%)	Part correlations
PHQ-9	0.491	0.000	[0.540-1.432]	0.141
SAS	0.330	0.04	[0.144-0.584]	0.064
Age	-0.215	0.015	[(-0.360)-(-0.041)]	0.045

The variable making the strongest unique contribution was the PHQ-9 scores, when the variance explained by all other variables in the model was controlled for. The SAS scores and age also made significant contributions with beta values of 0.330 and (-0.215), respectively. Higher PHQ-9 scores and higher SAS scores predicted higher PCL-C scores. Younger age groups scored higher on the measure of posttraumatic stress than older patients. Therefore, one year age value was significantly associated with lower PCL-C scale scores (B=-0.215, p=0.015).

Therefore, our model, which included PHQ-9 scores, SAS scores, and age, explains 63% of the variance in PCL-C post traumatic stress scores. Of these variables, PHQ-9 made the largest unique contribution.

Comparison of prevalences between the ICD group, mutation negative siblings group, and unaffected spouses group

In the larger study, 104 individuals submitted the completed questionnaire package including the 53 ICD patients, as well as 25 mutation negative siblings and 26 unaffected spouses. In this section, we compare the mean scores among the three groups.

Mean scores on each of the scales between the three groups (ICD group; mutation negative siblings group; unaffected spouses group) were compared via a one-way ANOVA, with group status as the independent variable, and each of the scale scores as the dependent variable.

Table 4.8: Group comparisons of PHQ-9, SAS, and PCL-C mean scale scores

ANOVA group comparisons	PHQ-9	SAS	PCL-C
ICD group mean	7.28 (6.41)	43.66 (12.15)	33.25 (12.87)
Negative siblings mean	4.64 (3.84)	36.52 (9.56)	27.04 (8.53)
Unaffected spouses mean	4.92 (5.28)	39.77 (9.72)	36.69 (14.35)
F-value	2.590	3.782	4.008
P-value	0.080	0.026	0.021

No statistically significant differences were found in PHQ-9 scores between the three groups *[F(2,101)=2.590, p=0.080]*. Therefore, depression score means were similar among the three groups in our analysis.

A one-way ANOVA was conducted to explore the impact of group status on anxiety symptom scores as measured by the Zung anxiety scale. There was a statistically significant difference at the $p<0.05$ level in SAS scores among the three groups *[F(2,101)=3.782, p=0.026]*. Post-hoc comparisons using the Turkey HSD test indicated that the mean score for the ICD group (M=43.66, SD= 12.15) was significantly higher from the mean score in the mutation negative siblings group (M=36.52, SD=9.56) with a mean difference of 7.14 scale points. The differences in mean scores between the ICD group and the spouses group was not statistically significantly.

Finally, a one-way between-groups analysis of variance was conducted to explore the impact of group status on posttraumatic stress symptom scores as measured by the PCL-C scale.
There was a statistically significant difference at the $p<0.05$ level in PCL-C scores among the three groups *[F(2,101)=4.008, p=0.021]*. Post-hoc comparisons using the Turkey HSD test indicated that the mean score for the unaffected spouses group (M=36.69, SD= 14.35) was significantly higher than the mean score in the mutation negative siblings group (M=27.04, SD=8.53). The ICD group did not differ significantly from the unaffected spouses group.

A Fishers exact test was completed to compare the proportions of positive depressive, anxiety, and posttraumatic stress symptoms among the three groups (ICD patients; mutation negative siblings; unaffected spouses).

Table 4.9: Fisher's exact test of group comparisons of scale proportions (PHQ-9, SAS, PCL-C) in the positive symptomatology range

N= 104 (3 groups)	Fisher's test statistic	Fisher's p-value (2-sided)	Pearson Chi-squared	Chi-squared p-value (2-sided)
PHQ-9 ≥10	4.008	0.129	4.412	0.122
SAS ≥45	3.511	0.173	3.608	0.173
PCL-C ≥36	13.948	0.001	14.333	0.001

The mean PHQ-9 score in the ICD group was 7.28, which is considered to be within the mild depressive symptom range. 15/53 respondents scored above the positive symptom threshold of 10 points, which signifies moderate depressive symptomatology.

For PHQ-9 scores ≥10 points [indicating a positive cut off for depressive symptoms], the Fisher's exact test statistic was 4.008 with a p-value of 0.129. The Pearson Chi-Square test statistic (4.412) similarly did not reach statistical significance (p=0.122). Therefore, the results indicate that there is no statistically significant difference between the three groups in terms of PHQ-9 test proportions ≥10 points.

The mean SAS score in the ICD group was 43.66, which is within normal limits. 26/53 respondents scored above the positive anxiety symptom threshold of 45 points, which represents mild to moderate anxiety levels.

For SAS scores ≥45 points [indicating a positive cut off for anxiety symptoms], the Fishers exact test statistic was 3.511 with a p-value of 0.173. The Pearson Chi-Square test statistic (3.608) also did not reach statistical significance (p=0.173). Therefore, the results indicate that there is no statistically significant difference between the three groups in terms of SAS test proportions ≥45 points.

The mean PCL-C score in the ICD group was 33.25, which represents a score of moderate to high posttraumatic stress symptoms. 17/53 respondents scored above the positive posttraumatic symptom threshold of 36 points, which represents a high severity of post traumatic stress symptomatology (and most closely corresponds to a clinical diagnosis of PTSD).

For PCL-C scores ≥36 points [indicating high level of posttraumatic stress symptoms], the Fishers exact test and Pearson Chi-squared were both statistically significant. The Fishers exact test statistic was 13.948, with a p-value of 0.001. Similar values were observed with the Pearson Chi-Squared, with a test statistic of 14.333 and a p-value of 0.001. The results indicate that there is a statistically significant difference between the three groups in terms of PCL-C test proportions ≥36 points. Using a cut off score of 44 points for the PCL-C scale (to identify a much higher

score threshold representing only severe posttraumatic stress symptoms) yielded an almost statistically significant result as well, with a Fishers exact test statistic of 5.346 and a p-value of 0.059 (Pearson chi-squared test statistic 5.214, p=0.075). Therefore, even at the highest, most robust possible cut off score, the differences in PCL-C score prevalences was trending to significant differences between the three groups. Using a low threshold cut off score of 30 points yielded a statistically significant result as well (8.766, P=0.011). This indicates that a significant proportion of ICD patients in this sample scored above clinical cutoffs for posttraumatic stress symptoms, in the mild, moderate and severe symptoms ranges.

Psychiatric sequelae and general population norms

Table 4.10: Comparison of our study sample with general population levels of mental illness

%	ICD group percentage (p-value)	General population norms (%): lifetime prevalence	General population norms (%): 12-month prevalence
Positive depressive symptoms	28.3 (0.001) [represented as PHQ-9 ≥10 points, moderate depressive symptoms]	11.3 [Major depressive episode/Major depressive disorder diagnosis]	4.7 [Major depressive episode/Major depressive disorder diagnosis]
Positive anxiety symptoms	49 (0.000) [represented as SAS ≥45 points, mild to moderate anxiety symptoms]	8.7 [GAD diagnosis]	2.6 [GAD diagnosis]
Positive posttraumatic stress symptoms	32 (0.000) [represented as PCL-C ≥36 points, high severity of PTSD symptoms]	8 [PTSD diagnosis]	

*Pearson, Janz, & Ali, 2013.

Mean scores on the PHQ-9 scale signified mild depressive symptoms in this sample, while mean scores on the Zung anxiety scale were within normal limits (although almost in the mild to moderate anxiety range). The mean score on the PCL-C scale represented moderate to high levels of posttraumatic stress symptoms. As indicated in the table, cut off score prevalences (considered positive for symptomatology of depression, anxiety, and posttraumatic stress) for each individual scale were higher than general population levels for corresponding symptomatology.

A binomial test indicated that the proportion of positive depressive symptoms (as measured by the PHQ-9 scale) of 28.3% in the ICD group was higher than the expected 11.3% in the general population for the lifetime prevalence of a major depressive episode, at p=0.001 (1-sided).

A binomial test indicated that the proportion of positive anxiety symptoms (as measured by the SAS scale) of 50% in the ICD group was higher than the expected 20% in the general population for the lifetime prevalence of all anxiety disorders combined, at p=0.000 (1-sided).

A binomial test indicated that the observed proportion of positive posttraumatic stress symptoms (as measured by the PCL-C scale) of 32% in the ICD group was higher than the expected 8% in the general population for lifetime prevalence of Posttraumatic stress disorder, at p= 0.000 (1-sided). Running a binomial test using the test proportion for PCL-C scores ≥44 points (a much

higher cut off threshold representing severe posttraumatic stress symptoms) observed that the observed proportion of 23% was also substantially higher than the expected general population proportion of 8%, at p=0.000 (1-sided).

ICD participants scoring in the highest score range on one of the questionnaires, or in the higher score ranges on multiple questionnaires were flagged for review. These individuals were contacted by the research team (as per original ethics protocol). This included contact by Dr. Kathy Hodgkinson, Dr. Orzylowski, Dr. Walsh, Dr. Paulin, Dr. Connors, or Dr Bassett, or contact made to the GP, and further follow up was arranged if deemed necessary. 14 (26%) of ICD participants were identified for mental health follow up due to high scores. Five individuals were contacted by myself and discussed further in the discussion section. Appropriate mental health follow up was discussed with each individual upon contact. There were no acute safety concerns and all individuals were agreeable to continue follow up with their primary care provider. No psychiatric diagnoses were made as these individuals did not undergo a complete psychiatric assessment.

CHAPTER 5: DISCUSSION

This is the first study of its kind to quantitatively explore psychiatric sequelae in the *TMEM43* p.S358L mutation positive ARVC ICD population. The unique psychosocial burdens of this patient group create an environment that warrants a specific research focus separate from that of non-genetic ICD populations. This study evaluated psychiatric sequelae (depressive, anxiety, and

posttraumatic stress symptoms) in *TMEM43* p.S358L mutation positive ARVC patients with an ICD. Mean scores on the mental health scales were within the normal range only with respect to anxiety symptoms. Mean scores were within the mild depressive range in the PHQ-9 (depressive) scores, but within the moderate to high range in PCL-C (posttraumatic stress) scores. In each of the scales, a substantial subgroup of patients had high prevalences of psychiatric sequelae. Clinically relevant levels of depression, anxiety, and posttraumatic stress were reported in 28.3%, 49%, and 32% of the participant cohort, respectively. Higher depressive scores were associated with higher anxiety and posttraumatic stress scores; higher anxiety scores were associated with higher depression and posttraumatic stress scores, as well as a higher number of appropriate ICD shocks; higher posttraumatic stress scores were associated with higher depressive and anxiety scores, as well as younger age. Collectively, these findings identify a higher prevalence of psychiatric sequelae of depression, anxiety and posttraumatic stress in the *TMEM43* p.S358L ARVC population with an ICD.

Psychological wellbeing and QOL in ICD patients have been extensively studied in those with ischemic cardiac disease (Dunbar et al., 2012; Sears & Conti, 2006; Thomas et al., 2009; Morris et al., 1991). This population generally involves older patients who have had ICDs for shorter periods of time. Despite the fact that ICDs save lives, several factors can present an ongoing challenge for patients, particularly those with an ICD indication for ARVC-related disease. Some challenges include a longer time course with the ICD, functioning and complications of the device, unpredictable discharges and high discharge rate, the genetic risks to family

members (and the burden of heredity) of ARVC, and the stigma of mental health, particularly in a population with prominent physical health issues at baseline (Versteeg et al., 2017; Rahmawati et al., 2013; Thylen et al., 2016). Studies identified increased rates of depression and anxiety after ICD implantation (Magyar-Russell et al., 2011). These studies increased the attention given to psychological factors in cardiac disease subgroups and in chronic illnesses.

Available studies in the ARVC ICD population have indicated poorer mental health and lower QOL parameters as compared to normative samples (James et al., 2012; Webster et al., 2014; Ingles et al., 2013). These studies assess groups of patients with ARVC where the genetic etiology is heterogenous: many different genetic types with variable phenotypic effect. The ICD ARVC population in NL with the *TMEM43* p.S358L mutation is homogeneous with respect to etiology, is of long standing in terms of the management and care within the health care system, and where accurate natural history and clinical course data has informed effective clinical management of family members at all stages of the disease. It was therefore important to assess this well ascertained population to see whether the same issues highlighted in other studies also occur in this population. The results of our study largely follow a similar pattern to previous literature, with higher than normal prevalences and mean scores of mental health sequelae (depression, anxiety, and posttraumatic stress).

Studies have reported upwards of 20% depressive symptoms at baseline in those with an ICD for primary implantation, from heterogenous causes (Amiaz et al., 2016); specific studies in ARVC

groups approximates a prevalence closer to 10% (James et al., 2012; Webster et al., 2014). Depressive symptoms were high in our ICD sample. The mean score on the PHQ-9 scale was 7.28, which fell within the mild depressive range. However, the proportion of individuals scoring positive on the PHQ-9 (a score of ≥10, which represents moderate depressive symptomatology) was much higher than would be expected in a normative sample. 28.3% of individuals scored positive in the ICD group, compared to a lifetime prevalence of major depressive disorder of 11.3% in a normative population sample (Pearson et al., 2013). The increased prevalence in our study cohort is in keeping with previous literature in ICD populations, and appears even higher than results recorded in other, more heterogenous ARVC populations. The genetic risks of the disease, and the poorer survival statistics in our participant cohort (prior to the introduction of the ICD) may cause further increased depressive symptoms in this population.

Increased anxiety symptoms have been evaluated in patients with ICDs, with most studies focused on those with ischemic heart disease; this trend has been identified in ARVC ICD groups as well. Clinically relevant anxiety in ARVC populations has been reported in some studies in up to 38% of patients, with ranges found between 25-38% (James et al., 2012; Webster et al., 2014; Ingles et al., 2013). Among the most common anxiety disorders in patients with ICDs were PTSD, phobias, somatoform disorders, generalized anxiety and panic (Rahmawati et al., 2013).

Despite the mean scores of the Zung anxiety scale falling in the normal range, the prevalence of mild to moderate anxiety symptoms in our sample was 49%, markedly higher than normative

samples in the population (20%), and also higher than previous literature in ARVC populations. Living with a disease with an unpredictable/variable/progressive clinical profile and having an ICD device with the potential for unexpected discharge events (that ultimately signify the appropriate or inappropriate cessation of a potentially terminal heart rhythm) could understandably cause a multitude of anxiety symptoms. Anxiety symptoms could range from restlessness, somatic pain, irritability, feelings of panic, an increased autonomic drive (resulting in a more frequently increased heart rate for instance), and sleep disturbances, as evident in the content of questions reflected on the Zung anxiety scale (Zung, 1971, 1974). These anxiety symptoms can correspond to a range of various possible anxiety disorders, but as a pattern best correspond to a diagnosis of generalized anxiety disorder and panic disorder (American Psychiatric Association, 2013).

Posttraumatic stress symptoms in ARVC ICD populations have not been well documented; the studies that do exist show a higher proportion of posttraumatic stress symptoms than a comparable general population. Ingles et al. (2013) showed the proportion of PTSD at 31% in a heterogenous ARVC sample. Considering the risk of SCD and the subsequent risk of experiencing unpredictable ICD shocks, it is not surprising that such individuals may be more prone to episodes of hyperarousal, psychological stress, avoidance of distressing memories, and negative alterations of cognition and mood, etc. as per the PTSD clinical criteria (American Psychiatric Association, 2013).

In our study cohort, the posttraumatic stress score mean and prevalence were substantially higher than normative samples. For example, the mean score on the PCL-C scale was 33.25, which represents moderate to high severity of PTSD symptoms. Similarly, the prevalence of individuals scoring above the 36 point cut off on the scale (representing high severity of PTSD symptoms) was 32%, substantially higher than the normative sample estimate of 8% (Pearson et al., 2013). Even at the highest scale cut off of 44 points (representing severe posttraumatic stress levels and a strong potential for a PTSD diagnosis), the prevalence was an alarming 23%.

It is difficult to compare scores on a scale with actual clinical psychiatric diagnosis, as they are not exactly equivalent comparisons. However, the scale score cut offs were chosen in such a way to provide the best comparison possible. Clearly, our ICD cohort had a substantially higher prevalence of depression, anxiety, and posttraumatic stress as compared to normative samples in the population.

Our study also explored demographic and clinical variables that could be associated with higher depressive, anxiety, and posttraumatic stress scales in our unique ARVC ICD population. Previous studies had identified several variables related to poorer mental health sequelae in ICD patients (in general populations and in heterogenous ARVC populations), including age, sex, increased ICD shock frequencies, time to first shock, comorbid medical conditions, and other ICD complications (Rahmawati et al., 2013; Thylen et al., 2016; Ingles et al., 2013). No previous studies were identified that looked at direct associations between various psychiatric

comorbidities- namely depression, anxiety and posttraumatic stress. In our study, severity of disease (represented by increased depressive, anxiety, and posttraumatic stress sequelae) correlated significantly with several variables.

Higher depressive symptoms on the PHQ-9 scale were strongly associated with higher anxiety scores on the SAS scale and higher posttraumatic stress scores on the PCL-C scale, but not with any other independent variables. The greater positive depressive symptomatology an individual reported, the greater likelihood that they would also report a higher amount of anxiety and posttraumatic stress symptoms. Over half the variance in depression scores (56%) was explained by other scale scores. Thus, participants scoring higher on the anxiety and posttraumatic stress scales were also more likely to score higher on the depressive scale.

The same relationship was revealed in anxiety and posttraumatic stress regression models, with the other mental health scale scores both significant predictors. Therefore, an individual's scale score on one mental health measure strongly influenced the scores on the other mental health measures. This is not surprising, as comorbidity in mental illness is the rule rather than the exception (Schaffer et al., 2012); therefore, having symptoms of depression, anxiety, and posttraumatic stress consequently increased an individual's risk of having psychiatric sequelae in all three symptom areas.

In addition to the scale scores' influence on each other, other variables were related to psychiatric sequelae. Prior research identified increased anxiety scores being correlated more strongly to female sex, younger age groups, and those with ICD complications (Ingles et al., 2013).

In our study cohort, higher anxiety scores were associated with increased number of appropriate shocks from the ICD device, which was statistically significant in the univariate analysis ($R=0.335$, $p=0.022$), but did not reach significance in the regression analysis. There was also a trend towards association for number of hospitalizations, but this did not reach statistical significance.

Nonetheless, increased anxiety levels related to a greater number of appropriate shocks exemplifies the unique fears that patients have related to the discharge of their device. An increased number of appropriate discharges from the ICD is directly related to a greater severity of disease, as each appropriate discharge represents an aborted ventricular arrhythmia and possible SCD. The occurrence of an ICD shock is often a significant traumatic event for a patient at any age, being both potentially physically painful (if the patient does not lose consciousness) and a reminder of the potentially lethal underlying heart condition (Sears & Kirian, 2010). Previous literature has suggested that high frequency of defibrillator discharge (and in some cases even a single shock) may be associated with psychological impairments (Carroll & Hamilton, 2005; Bostwick & Sola, 2007; Bilge et al., 2006; Van den broek et al., 2008; Passmann et al., 2007; Jacq et al., 2009; Redhead et al., 2010; Godemann et al., 2004).

Prevalences of anxiety in these varied ICD population studies ranged from 16%- 38%. Two studies involving heterogenous ARVC populations reported significantly higher anxiety scores in individuals who had experienced at least one shock from the ICD device and younger age (Rhodes et al., 2017).

Increased risk of distress, and particularly posttraumatic stress symptoms, have been reported in previous ICD literature. Prevalences in studies examining PTSD in ICD populations range between 12%-35%, with variable changes in symptoms over time (both increases and decreases have been reported) (Marshall et al., 1988; von Kanel et al., 2011; Habibovic et al., 2017; Kapa et al., 2010). Previous studies have suggested the following demographic and clinical factors associated with increased PTSD: young age, female sex, presence of comorbid medical conditions, and increased ICD complications (von Kanel et al., 2011; Habibovic et al., 2017; Kapa et al., 2010). These studies used heterogenous ICD populations, with a few including ARVC populations in particular. In addition, little is known about PTSD in younger patient cohorts. Several studies have reported worse QOL, increased anxiety and poorer functioning in those under 35 years of age (considered the younger age cohort) (James et al., 2012; Rhodes et al., 2017). Posttraumatic stress scores have significant clinical implications, and have been associated with poor compliance with medical recommendations, poor health behaviours such as smoking and physical inactivity, and increased morbidity and mortality, highlighting the need to identify patients who may be susceptible to emotional difficulties (van den Berk-Clark et al., 2018; Xue et al.,

2012; Karatzias & Chouliara, 2009).

In our ARVC ICD population, the age range was 22-71 years old, and the mean age of the group was 48.5. In our sample, higher posttraumatic stress scores were associated with younger age. Importantly, the age distribution in our ICD sample was most pronounced in middle age groups, suggesting that our data might actually underrepresent the actual impairment in the younger age cohort receiving this device. Notably, there is a large proportion of families in the study who are some of the oldest known families affected by this disease, in which several younger family members died young (and ultimately how these families came to the attention of clinicians in the first place). Therefore, these families are more likely to have ICD patients in middle age based on the time of discovery of the *TMEM43* p.S358L mutation and ICD treatment options, with their children not yet old enough for ICD consideration. Furthermore, the standard multiple regression model was statistically significant, and accounted for approximately 63% of the variance in PCL-C scores influenced by the PHQ-9 scores, the SAS scores, and age. Although age did not have as much of a unique contribution as compared to the other scale scores, it was nonetheless moderate and unique, with a beta value of (-0.215) and p=0.015. Since younger aged individuals received the ICD device more recently than older patients, it is possible that the association with higher posttraumatic stress symptoms is based on the psychologically traumatic event of ICD implantation being a more recent memory for these younger individuals as compared to their older counterparts. However, we would expect to see this trend in anxiety (and possibly

depressive) symptoms as well, but we do not. There was also a trend towards significance for number of appropriate shocks [from the ICD device] (R=0.287, p=0.051); having increased number of appropriate ICD shocks trended towards having higher posttraumatic stress scores.

Total variance contributed by the independent variables on each of the scales ranged between 50-63% in all of the regression models, indicating strong contributions from the variables to the total model, but also suggesting that other unknown (or unmeasured) factors contributed to the scores. It is clear that each of the scales had the most significant, independent effect on the other scales, with only small contributions from other independent variables, such as age, number of appropriate shocks, and trends towards significance for number of hospitalizations.

Notably, considering findings from previous literature suggesting female sex to be an independent risk factor for poorer mental health in ICD populations, and females found to be more severely affected by psychiatric symptoms compared to their male counterparts (Rahwamati et al., 2013; Versteeg et al., 2017; Bostwick & Sola, 2007; Bilge et al., 2006; Vasquez et al., 2008; Brouwers, van den Broek, Denollet, & Pedersen, 2011), we did not find significant correlations between female sex and increased scale scores, despite the sample population being made up of 66% women. Furthermore, in our population, we expected that males, having earlier risk of symptom onset (and therefore earlier age of ICD implantation, mean age 29.8 years old), and a more malignant disease course, may have been more strongly negatively affected by the

disease course. Consequently, male sex was also not correlated with significant findings. There are several possible reasons we did not see significant results based on sex in our study sample. Other than small sample size possibly under powering our study, there were fewer males in the sample. Less male representation could be due to less recruitment potential via ICD clinic or phone or less successful recruitment into the study if contact was made. Although we are unaware of specific health care follow up participation in the *TMEM43* p.S358L ARVC ICD patients (due to patient confidentiality reasons), health care data generally supports poorer health care compliance in males (Ogrodniczuk, Oliffe, Kuhl, & Gross, 2016; Clement et al., 2015). Furthermore, the stigma of mental health is a real and serious concern, and although minimizing mental health concerns is not uncommon, it is a particularly higher occurrence in males. Therefore, these may be some of the potential reasons we were unable to see a significant association with sex in our study. Interestingly, outliers with the highest scores on the PCL-C were all female. These encompassed mostly younger age groups (range 22-50); they also tended to score high on the SAS scale, but not the PHQ-9.

Our study also compared psychiatric sequelae between several groups: the ICD patient group, the mutation negative siblings group (born at *a priori 50%* risk of the disease), and the genetically unaffected spouses group. The mean scores on the scales for the ICD group were evaluated and compared to the mean scores of the other two groups using a one-way ANOVA test. No statistically significant differences were found in the PHQ-9 mean scores between the three groups, although anxiety scores did differ. Patients in the ICD group had higher anxiety scores than the

mutation negative siblings, while the mean scores did not differ statistically from the unaffected spouses group. Posttraumatic stress scale scores also differed among the groups, such that unaffected spouses showed greater posttraumatic stress than mutation negative siblings, but not from ICD patients. The comparison between the mean scores in the three groups appears to show that mutation negative siblings had the lowest scores on all three of the mental health scales, as compared to the ICD group and the spouses group. We expected the mean scores to be highest in the ICD group. While this was clearly apparent in the anxiety and depression scores, posttraumatic stress was highest in the spouses group. Although we expected high results in the ICD group, it is not surprising that spouses, who are most likely to be direct witnesses of ICD shocks in their partners, would also score high on the posttraumatic stress parameter.

The prevalences of positive posttraumatic stress symptoms in the ICD group, mutation negative siblings group, and unaffected spouses group were 32%, 16%, and 65%, respectively. For the PCL-C results, although the ICD group comprised the largest number of individuals scoring positive on the PCL-C test (17/53), the group with the highest proportion of individuals scoring positive on the PCL-C test were the unaffected spouses (65%). In comparison, the negative siblings group scored very low overall on this scale with only four respondents scoring in the positive range. There was a statistically significant difference in PCL-C prevalences between the ICD group and the mutation negative siblings group showing that posttraumatic stress symptom prevalences were statistically higher in the ICD group as compared to the mutation negative

siblings group.

Prevalences of *clinically* relevant symptoms of depression, anxiety, and posttraumatic stress were also compared between the three groups (using cut off scores for clinically relevant symptomatology). The ICD group had higher prevalences on the depression (28.3%) and anxiety (49%) scales compared to spouses or negative siblings, while the unaffected spouses group had the highest proportion of posttraumatic stress symptomatology of the three groups (65%).

The spousal group having the highest average mean scores and highest prevalence of posttraumatic stress symptoms among the three groups is an important finding, as we had predicted that all psychiatric sequelae would be highest in the ICD group. Only a few studies have explored the effects of ICD implantation on spouses of patients. These have focused on cardiac disease patients, including those who received the ICD for primary and secondary indications. Literature has shown that spouses' mental health is affected by their partners' ICD. Increased anxiety, depression and psychological distress has been reported; frequently, the partner's level of anxiety was higher than that of the ICD patient (Van den broek et al., 2008; Redhead et al., 2010; Ladwig et al., 2008; Rottmann et al., 2018; Pedersen et al., 2009). Some studies report upwards of 30% of partners of ICD patients suffer from depression and anxiety (Rottmann et al., 2018). Qualitative evidence in family members of patients with ICDs in our local population also revealed significant psychological sequelae (Etchegary et al., 2016). While we had predicted that ICD patients would score highest on mental health measures, mental health concerns

were not unexpected in the spouses group. There are several potential reasons for this. Firstly, spouses often share a close environment with their partner, and due to this proximity, they are constantly experiencing the stress of the ARVC disease and its ICD treatment implications at almost as close of a proximity as the ICD patients themselves. Any shocks or complications from the ICD device would be witnessed by them in close proximity. Spouses often see the results of the ICD shock more directly than the ICD patients themselves (who may lose consciousness due to poor cardiac perfusion). This experience can include seizure activity, loss of consciousness, loss of bodily functions, and the inherent fear of impending death. This could certainly cause great distress in anyone who witnesses such an event, but even more so in someone close to the victim. The closeness of the relationship between the ICD patient and spouse also likely plays a role in these findings. Spouses may be more emotionally invested in their partners' well-being, and the potentially stronger emotional bond between them may make spouses particularly more vulnerable to stress related to the ICD device and its implications. In the *TMEM43* p.S358L cohort in particular, several families live in rural parts of the province, with access to emergency services more strained; frequent health care complications also cause additional financial and economic strain on the families.

Concurrently, the effects of posttraumatic stress symptoms in the ICD group itself cannot be minimized. Despite the unaffected spouses group having a higher prevalence of symptoms when compared to the other groups, ICD patients still experienced high levels of distressing symptoms. These are individuals at high risk of PTSD and should be monitored closely. In contrast, the

mutation negative siblings, although genetically related, may be physically at a distance (as many would not be living in the same house or indeed province as their sibling), meaning they do not directly experience the same stressors as the ICD patients and their spouses.

The *TMEM43* p.S358L mutation positive ARVC patients with an ICD have higher prevalences of depression, anxiety and posttraumatic symptoms compared to the general population. In any clinical population, screening of psychiatric sequelae is important; clearly, this is even more important in our unique population. Our study clearly shows the importance of screening and recommends follow up for mental health sequelae. Notably, mental health scales alone cannot provide a diagnosis of mental illness; a structured clinical interview is deemed necessary. However, screening measures help identify those who may need further psychiatric referral. In addition, all of the scale scores were strongly associated with one another; therefore, an increased score on one of the mental health scales strongly increased an individual's likelihood of scoring high on the other scales. This is not surprising, considering the high proportion of mental illness comorbidities and the overlap of clinical features between depressive, anxiety and posttraumatic stress symptoms.

Anxiety and posttraumatic stress symptoms were the most pronounced symptoms in our sample group, with the highest prevalence and associations with several independent variables other than the scale scores. Decreased age was associated with higher posttraumatic stress symptoms and made a significant unique contribution to the scale scores in the multiple regression model.

Greater numbers of appropriate shocks [from the ICD device] were associated with higher anxiety scores. Anxiety had the largest proportion of higher scores above the cut off value (nearly 50%), and was the only scale associated with a specific clinical variable that could be assessed and monitored, namely the number of appropriate shocks.

Side effects and complications of the device need to be monitored closely. These include appropriate discharges (to stop an abnormal rhythm) and inappropriate discharges, which would be considered device malfunctions or a programming issue (the device recognizing a fast normal rhythm as abnormal). In the *TMEM43* p.S358L population, ICD complications and side effects related to the device do not occur infrequently. These can range from malfunctions in the device itself (such as wear and tear of the device rendering a replacement necessary), as well as inappropriate shocks. Although not considered a device complication or malfunction, an appropriate shock from the device can be a stressful and physically and psychologically painful event. Therefore, aside from actual side effects from the device, even the appropriate function of the device can cause a range of adverse effects as well. An estimated 20% of the cohort had repeated appropriate discharges, and 6% had repeated inappropriate discharges (Hodgkinson et al., 2016). These adverse effects of the device can particularly affect younger recipients of the ICD, who may be more vulnerable to stress, and for whom the ICD treatment course is longer (Romero et al., 2013).

A number of key studies have highlighted the effectiveness of the ICD in prevention of SCD in

genetic heart disease cohorts, and it remains a cornerstone of clinical management (Maron et al., 2007; Bhonsale et al., 2011; Schwartz et al., 2010). It is especially effective, and the only known treatment, in our specific *TMEM43* p.S358L mutation positive cohort. Despite the clear survival benefit of the ICD [especially in our *TMEM43* p.S358L study cohort], the ICD may be associated with deleterious psychological effects, even in the absence of medical complications. Depression, anxiety, and posttraumatic stress are the mental health sequelae that we have identified in our study population. However, the emotional distress of having an ICD is related to all-cause, as well as cardiac-related mortality. Therefore, psychological symptoms that present in a proportion of ICD patients should not be underestimated (Rahmawati et al., 2013). With the implantation of an ICD, clinicians should be alert and aware of the potential adverse psychological impacts of the implant; in particular, depression, anxiety, and posttraumatic stress. This is especially true in younger individuals, and those experiencing a more severe clinical course, based on increased numbers of appropriate discharges of the ICD and increased numbers of hospitalizations.

In addition, a positive screening on one mental health parameter, for example depression, should highly alert the clinician to possible additional psychiatric sequelae, specifically anxiety and posttraumatic stress, which should be screened appropriately, with appropriate psychiatric referrals where warranted. The *TMEM43* p.S358L patient population is used to a lot of clinical attention related to their cardiac condition and the parameters of their ICD device. Mental health screening is not part of the typical ICD follow up appointment, and it is rare for patients to be regularly screened for symptoms of depression, anxiety, or posttraumatic stress. Our results

suggest a greater need for a more holistic and comprehensive clinical approach in this population.

These results should lead to further discussions regarding provision of care in this population; this signals the importance of offering patients access to targeted interventions, including psychological care and support for both patients and their spouses. Not all patients receiving an ICD get the same therapeutic benefit and have the same risk of psychiatric side effects. In our study, certain variables associated with ICD patients may have made them more vulnerable to developing depression, anxiety, and posttraumatic stress symptoms, and may therefore benefit from additional psychological support, pre- and post-ICD therapy. Future research is needed to identify what these variables are and how best to screen for them.

Long term support and interventions should be implemented for effective management of ICD patients, with ongoing strategies to promote positive general health behaviour, medication compliance, psychoeducation, and resilience. Multidisciplinary collaboration will be a crucial part in assessment of patients, to ensure appropriate follow up management in accordance with ICD protocols and mental health treatments, be it non-pharmacological and pharmacological. Cardiac rehabilitation programs, cardiac genetic counselling, psychological therapy, and structured psychological group interventions are just some of the interventions with positive evidence in addressing mental health sequelae in similar populations (Vasquez, Conti, & Sears, 2010; Belardinelli, Capestro, Misiani, Scipione, & Georgiou, 2006; Sears et al., 2007).

Increased levels of depression, anxiety, and posttraumatic stress symptoms occur at a disproportionately higher rate in this patient population. In addition to the observed increased likelihood of comorbidity between depressive, anxiety, and posttraumatic stress symptoms, other independent factors associated with poorer mental health included having a greater number of appropriate shocks from the ICD device, and younger age. Furthermore, a higher prevalence of posttraumatic stress symptoms occurs in spouses of ICD patients as well.

Brief screening measures related to patients' and partners' psychiatric concerns should be implemented in an outpatient setting. Patients with multiple risk factors (i.e., positive mental illness screens, younger age, high ICD discharge rate) can be screened more closely and provided with a more robust opportunity to discuss concerns; a psychiatric referral may be considered. An anticipatory discussion regarding higher risk groups may be appropriate in younger age groups, who may benefit from early intervention and support in particular. These discussions can occur in a clinical setting with spouses involved, where all potential mental health concerns can be addressed and managed. This is critical because most ICD patients live in a family setting, with care provided to them by the spouse if needed. This inherited cardiac disease in one way or another likely affects all household family members. A disease associated with SCD can make all family members vulnerable to depression, anxiety, and posttraumatic stress symptoms, with difficulties adjusting to this chronic illness.

A small proportion of ICD patients scored in a very high range on the questionnaires. When this

event occurred, as per submitted ethics protocol, these individuals were contacted by a team member and further follow up was discussed. Due to confidentiality reasons, specific follow up details will not be discussed. However, in a few instances, Dr. Walsh and Dr. Orzylowski were involved in psychiatric supportive care for these individuals and appropriate long term follow up options were discussed. In our specific patient setting, this usually involved appropriate psychiatric referral through the patient's family physician where continuity of care was most complete. Crisis intervention and emergency services were also discussed. Of note, none of the contacted individuals required immediate psychiatric emergency care at time of contact, and all were willing and able to follow up with appropriate services suggested by the care team.

The outcome of the current study reflects a real life clinical setting in this specific subtype of ARVC in Newfoundland and Labrador. The results show that the majority of individuals with an ICD due to a *TMEM43* p.S358L positive mutation have difficulties adjusting to the device as reflected in the higher mean scores and prevalences of depressive, anxiety, and posttraumatic stress symptoms in this population. Subsequently, spouses of ICD recipients also appear to be disproportionately affected by posttraumatic stress symptoms, given the proximity they have to traumatic events with respect to their spouses. On the contrary, it appears mutation negative siblings are minimally (if at all) affected by depression, anxiety, and posttraumatic stress symptoms.

The *TMEM43* p.S358L mutation positive ARVC ICD patient group has been studied extensively since 1998 and can provide ongoing insights into the characteristics of this disease process and

its psychological effects. Future research related to QOL in the family setting, and further possible associated variables that may be related to poorer mental health would provide additional insight into our current findings. The results of our study can hopefully advocate for the implementation of mental health screening and management in this unique clinical group. They must come to terms with their diagnosis to a cardiac disease at a much younger age, understand the inheritance risk to family members, make decisions regarding genetic testing of their children, and this often on a background of previous SCD in the family. This uniquely homogenous ARVC population can provide vital and robust details about this disease in ways that variable heterogenous populations cannot.

Limitations

There were several limitations in our study. Our retrospective cohort study can only elucidate possible associations between variables and outcomes; we cannot conclude cause and effect of variables on the mental health parameters of our ICD population. Although the sample size was a sample of convenience, we had a 65% participant rate in the ICD group. Although this is a good representation, this could have been more robust, which may have revealed further associations with the scale scores that we simply did not observe due to our sample size of 53 participants (risk of smaller effect size). It would be relevant to know potential characteristics of individuals who were approached but refused to participate in the study. The collection of data must also be examined, considering the option of in-person vs. mail in packages, as this introduces response

bias. Given the stigma of mental health, individuals completing the questionnaires in person may have felt more pressured to complete the package in a timely manner, but fearing stigma, avoided truthfully answering certain questions. A similar bias may have occurred in those who mailed in their packages, if they included return postage they may have feared identification through the packages and not answered truthfully. We also must consider (as with any self-rated mental health research) that individuals who may have had worse psychiatric sequelae specifically chose not to participate in our study for fear of stigma. This was particularly difficult with families undergoing difficult medical complications from their ARVC disease who were not contacted out of respect, but would likely have been helpful information for the study cohort. Furthermore, given the breadth of information available in the secondary database, we only looked at a limited amount of the variables. We could have analyzed more variables that may have provided us with more information.

The mental health scales chosen for our study were all self-rated. This was done mainly for time management purposes, as it would have been more difficult and more time consuming to have clinician rated scales involved. Self-rated scales have a higher risk of introducing response bias, with the possibility that individuals concerned with psychiatric stigma underreported depressive, anxiety, and posttraumatic symptoms. Although the goal of our study was to analyze this specific *TMEM43* p.S358L ARVC population, our homogenous study population limits the generalizability of our results, as this particular type of ARVC is clinically unique as compared to other genetic types of ARVC; in particular, this genetic subtype has a more malignant clinical course, and

therefore may not exhibit the same mental health outcomes when compared to other ARVC ICD populations.

Anxiety scores and posttraumatic stress scores were associated with certain variables directly related to the ICD. However, depression scores were not, and were only associated with the other scale scores. The lack of robust correlation to direct ICD device variables limits our understanding of the elevated depression results and their etiology. Given the lack of an outside control group completely unaffected by ARVC and the ICD device, it is difficult to elucidate the underpinnings of increased depression in the ICD cohort, and may be due to the disease itself, irrespective of the actual ICD device. This could also be considered for the anxiety scores, albeit to a lesser degree. We approach our results with caution given our small sample size and lack of an independent control group and are careful not to put too strong of an emphasis on the ICD device as the main or only contributor to psychiatric sequelae in this unique population.

CONCLUSION

This study measured psychiatric sequelae of depression, anxiety, and posttraumatic stress symptoms in *TMEM43* p.S358L mutation positive ARVC ICD patients in NL, Canada. This study was part of a larger project looking at the psychiatric sequelae among this ARVC ICD group and their family members. It is the first quantitative study of its kind in this specific patient population and in their family members, namely their mutation negative siblings, and unaffected spouses. This

study focus was the ICD recipients. Previous literature has reported findings consistent with increased symptoms of depression, anxiety, and posttraumatic stress in heterogenous ARVC ICD populations.

The ICD study cohort's scale score means and prevalences were analyzed and compared to general population normative values as well as to the other groups in the larger study (mutation negative siblings and unaffected spouses). Scale scores were also analyzed with several independent variables to assess whether certain variables of disease severity were associated with higher scale scores. Variables assessed were the scale scores, age, sex, first degree relative with SCD or heart transplant, method of diagnosis, presyncope and/or syncope and/or palpitations, sex of transmitting parent, heart transplant status, age at ICD implantation, number of hospitalizations, and number of appropriate and inappropriate shocks.

Findings from our study were in keeping with previous literature, and consequently showed substantially higher rates of depression, anxiety, and posttraumatic stress symptom prevalence in our ICD population as compared to general population normative values and in comparison to their mutation negative siblings and spouses, with the exception of the spouses group having the highest prevalence of posttraumatic stress among the three groups. Variables associated with disease severity and higher scale scores included each particular scale score having an impact on the risk of scoring high on a subsequent scale. Additionally, increased anxiety scores were associated with an increased amount of appropriate shocks from the ICD device, and higher posttraumatic

stress scores were associated with younger age. Only the scale scores and age were found to be significant and have a unique contribution on scale scores in the multiple regression analysis. Mean scores on the scales were above the normal range in depressive and posttraumatic stress symptoms, most pronounced in posttraumatic stress symptomatology with mean scores in the high severity range. Only mean scores on the anxiety scale were within normal limits, albeit bordering on the mild anxiety range. ICD patients' scale score prevalences were also markedly higher than general population norms. ICD patients also had higher prevalences of depression and anxiety among the three groups, but posttraumatic stress symptoms were slightly more prevalent in the spouses of ICD patients.

Future research initiatives could include further exploration of contributing ICD variables, larger sample sizes with an independent control group, and the assessment of similar ARVC population without an ICD, as to better elucidate the scope and impact of varying contributions of disease aspects on the mental health of these individuals.

This study provides important information (and first of its kind) regarding mental health sequelae in the *TMEM43* p.S358L mutation positive ARVC ICD patient population in NL. Despite the clear survival benefit of the ICD in this population, our results clearly highlight the high psychological burden accompanying this population. Further research would be of benefit in this unique patient cohort, to better understand the drivers of psychiatric sequelae and inform interventions.

Bibliography and References

Ahmad F., Li D., Karibe A., et al. (1998). Localisation of a gene responsible for arrhythmogenic right ventricular dysplasia to chromosome 3p23. *Circulation, 98*, 25, 2791-5. DOI: 10.1161/01.cir.98.25.2791.

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed, Text Revision). Arlington, VA.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA.

Amiaz R., Asher E., Rozen G., Czerniak E., Glikson M., & Weiser M. (2016). Do implantable cardioverter defibrillators contribute to new depression or anxiety symptoms? A retrospective study. *International Journal of Psychiatry,* 20, 101-105. doi: 10.3109/13651501.2016.1161055.

Amiaz R., Asher E., Rozen G., et al. (2017). Reduction in depressive symptoms in primary prevention ICD scheduled patients - One year prospective study. *General Hospital Psychiatry,* 48, 37-41. DOI: 10.1016/j.genhosppsych.2017.06.013.

Arnous S., Murphy N.F., Pyne-Daly P., et al. (2011). Clinical and psychological impact of prophylactic implantable cardioverter-defibrillators in a community heart failure population. *Ireland Journal of Medical Sciences, 180*, 2, 369-374. DOI: 10.1007/ s11845-010-0659-z.

Azaouagh A., Churzidse S., Konorza T., & Erbel R. (2011). Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a review and update. *Clinical Research in Cardiology,100*, 5, 383-394. DOI: 10.1007/s00392-011-0295-2.

Basso C., Pilichou K., Bauce B., Corrado D., & Thiene G. (2018). Diagnostic Criteria, Genetics, and Molecular Basis of Arrythmogenic Cardiomyopathy. *Heart Failure Clinics, 14*, 2, 201-213. DOI: 10.1016/j.hfc.2018.01.002.

Beery T.A., Baas L.S., & Henthorn C. (2007). Self-reported adjustment to implanted cardiac devices. *Journal of Cardiovascular Nursing, 22*, 6, 516-24. DOI: 10.1097/01.JCN. 0000297390.11324.46.

Belardinelli R., Capestro F., Misiani A., Scipione P., & Georgiou D. (2006). Moderate exercise training improves functional capacity, quality of life, and endothelium-dependent vasodilation in chronic heart failure patients with implantable cardioverter defibrillators and cardiac resynchronization therapy. *European Journal of Cardiovascular Prevention and Rehabilitation, 13*, 5, 818-25. DOI: 10.1097/01.hjr.0000230104.93771.7d.

Bhonsale A., James C.A., Tichnell C., et al. (2011). Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention. *Journal of American College of Cardiology, 58*, 14, 1485-96. DOI: 10.1016/j.jacc.2011.06.043.

Bilge A.K., Ozben B., Demircan S., et al. (2006). Depression and anxiety status of patients with implantable cardioverter defibrillator and precipitating factors. *Pacing and Clinical*

Electrophysiology, 29, 6, 619-626. DOI: 10.1111/j.1540-8159.2006.00409.x.

Blanchard E.B., Jones-Alexander J., Buckley T.C., & Forneris C.A. (1996). Psychometric properties of the PTSD checklist (PCL). *Behavioral Research & Therapy, 34,* 8, 669-673. DOI: 10.1016/0005-7967(96)00033-2.

Bostwick J.M., & Sola C.L. (2007). An Updated Review of Implantable Cardioverter/ Defibrillators, Induced Anxiety, and Quality of Life. *Heart Failure Clinics, 30*, 4, 677-88. DOI: 10.1016/j.psc.2007.07.002.

Brouwers C., van den Broek K.C., Denollet J., & Pedersen S.S. (2011). Gender disparities in psychological distress and quality of life among patients with an implantable cardioverter defibrillator. *Pacing and Clinical Electrophysiology, 34*, 7, 798-803. DOI: 10.1111/j. 1540-8159.2011.03084.x.

Carroll D.L., Hamilton G.A., & Kenney B.J. (2002). Changes in health status, psychological distress, and quality of life in implantable cardioverter defibrillator recipients between 6 months and 1 year after implantation. *European Journal of Cardiovascular Nursing, 1*, 3, 213-9. DOI: 10.1016/S1474-5151(02)00040-3.

Carroll D.L. & Hamilton G.A. (2005). Quality of life in implanted cardioverter defibrillator recipients: the impact of a device shock. *Heart Lung, 34*, 3, 169-178. DOI: 10.1016/ j.hrtlng.2004.10.002.

Carroll D.L. & Hamilton G.A. (2008). Long-term effects of implanted cardioverter defibrillators on health status, quality of life, and psychological state. *American Journal of Critical Care, 17*, 3, 222-230. PMID: 18450679.

Ceccarini M., Manzoni G.M., & Castelnuovo G. (2014). Assessing Depression in cardiac patients: What measures should be considered? *Depression Research and Treatment, 148256*. DOI: 10.1155/2014/148256.

Choudhary N., Tompkins C., Polonsky B., et al. (2016). Clinical Presentation and Outcomes by Sex in Arrhythmogenic Right Ventricular Cardiomyopathy: Findings from the North American ARVC Registry. *Journal of Cardiovascular Electrophysiology, 27*, 5, 555-562.

Cleland J.G., Ghosh J., Freemantly N., et al. (2003). Clinical trials update and cumulative meta-analysis from the ACC: WATCH, SCD-HeFT, DIMAM, CASINO, STRATUS-US, RIO-Lipids and cardiac resynchronization therapy in heart failure. *European Journal of Heart Failure, 6*, 4, 501-8. https://doi.org/10.1016/j.ejheart.2004.04.014.

Clement S., Schauman O., Graham T., et al. (2015). What is the impact of mental health-related stigma on help-seeking? A systematic review of quantitative and qualitative studies. *Psychology and Medicine, 45*, 1, 11-27. DOI: 10.1017/S0033291714000129.

Corrado D., Wichter T., Link M., et al. (2015). Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: An international task force consensus statement. *European Heart Journal, 36*, 46, 3227-3237.

Crossmann A., Pauli P., Dengler W., Kuhlkamp V., Wiedemann G. (2007). Stability and cause of anxiety in patients with an implantable cardioverter-defibrillator: A longitudinal two-year follow-up. *Heart Lung, 36*, 2, 87-95. DOI: 10.1016/j.hrtlng.2006.08.001.

de Ornelas Maia A.C.C., Soares-Filho G., Pereira V., Nardi A.E., & Silva A.C. (2013). Psychiatric disorders and quality of life in patients with implantable cardioverter

defibrillators: A systematic review. *Primary Care Companion CNS Disorders, 15*, 2, PCC.12r01456. DOI: 10.4088/PCC.12r01456.

Deyell M.W., Tung S., & Ignaszewski A. (2010). The implantable cardioverter-defibrillator: From Mirowski to its current use. *British Columbia Medical Journal, 52,* 5, 248.

Dunbar S.B., Kimble L.P., Jenkins L.S., et al. (1999). Association of mood disturbance and arrhythmia events in patients after cardioverter defibrillator implantation. *Depression and Anxiety, 9,* 4, 163-8. DOI: 10.1002/(sici)1520-6394(1999)9:4<163::aid-da3>3.0.co;2-b.

Dunbar S.B., Dougherty C.M., Sears S.F., et al. (2012). Educational and Psychological Interventions to Improve Outcomes for Recipients of Implantable Cardioverter Defibrillators and Their Families. A Scientific Statement from the American Heart Association.*Circulation, 126*, 17, 2146-2172. DOI: 10.1161/CIR.0b013e31825d59fd

Dunstan D.A., Scott N., & Todd A.K. (2017). Screening for anxiety and depression: Reassessing the utility of the Zung scales. *BMC Psychiatry, 17*, 1, 329. DOI: 10.1186/ s12888-017-1489-6.

Dunstan D.A., & Scott N. (2018). Assessing clinical significance and symptom severity using the Zung scales: Levels of misclassification arising from confusion between index and raw scores. *Depression Research and Treatment, 2018*, 9250972. DOI: 10.1155/2018/9250972.

Etchegary H., Enright G., Audas R., et al. (2016). Perceived economic burden associated with an inherited cardiac condition: a qualitative inquiry with families affected by arrhythmogenic right ventricular cardiomyopathy. *Genetics in Medicine,* 18, 584-592.

Etchegary H., Pullman D., Connors S., et al. (2017). *"There are days I wish I wasn't there, and there's days I realize I'm lucky"*: A qualitative study of psychological sequelae to the Implantable Cardioverter Defibrillator as a treatment for the prevention of sudden cardiac death in Arrhythmogenic Right Ventricular Cardiomyopathy. *JRSM Cardiovascular Disorders*, 6, 1-9.

Godemann F., Butter C., Lampe F., et al. (2004). Panic disorders and agoraphobia: Side effects of treatment with an implantable cardioverter/defibrillator. *Clinical Cardiology, 27*, 6, 321-6. DOI: 10.1002/clc.4960270604.

Gonzalez-Torrecilla E., Arenal A., Atienza F., et al. (2015). Current indications for implantable cardioverter defibrillators in non-ischemic cardiomyopathies and channelopathies. *Rev Recent Clinical Trials, 10*, 2, 111-27. DOI: 10.2174/1574887110666150407104312.

Gostoli S., Bonomo M., Roncuzzi R., et al. (2016). Psychological correlates, allostatic overload and clinical course in patients with implantable cardioverter defibrillator (ICD). *International Journal of Cardiology, 220*, 360-4 DOI: 10.1016/j.ijcard.2016.06.246.

Guiraudon G.M., Klein G.J., Gulamhusein S.S., et al. (1983). Total disconnection of the right ventricular free wall: surgical treatment of right ventricular tachycardia associated with right ventricular dysplasia. *Circulation, 67*, 2, 463-740. DOI: 10.1161/01.cir.67.2.463.

Guttmann O.P., Mohiddin S.A., & Elliott P.M. (2014). Almanac 2014: Cardiomyopathies. *Heart, 100*, 10, 756-64. DOI: 10.1136/heartjnl-2013-305420.

Habibovic M., Denollet J., Pedersen S.S., et al. (2017). Postraumatic stress and anxiety in patients with an implantable cardioverter defibrillator: Trajectories and vulnerability

factors. *Pacing and Clinical Electrophysiology, 40*, 7, 817-823. DOI: 10.1111/pace13090.

Haddad M., Walters P., Phillips R., et al. (2013). Detecting depression in patients with coronary heart disease: A diagnostic evaluation of the PHQ-9 and HADS-D in primary care, findings from the UPBEAT-UK Study. *PLoS One, 8*, 10, e78493. DOI: 10.1371/journal.pone.0078493.

Hammash M.H., Hall L.A., Lennie T.A., et al. (2013). Psychometrics of the PHQ-9 as a measure of depressive symptoms in patients with heart failure. *European Journal of Cardiovascular nursing, 12*, 5, 446-53. DOI: 10.1177/1474515112468068.

Hodgkinson, K.A., Parfrey P.S., Bassett A.S., et al. (2005). The impact of implantable cardioverter-defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). *Journal of the American College of Cardiology, 45, 3,* 400-408.

Hodgkinson K., Dicks E., Connors S., et al. (2009). Translation of research discoveries to clinical care in arrhythmogenic right ventricular cardiomyopathy in Newfoundland and Labrador: Lessons for health policy in genetic disease. *Genetics in Medicine, 11*, 12, 859-865. DOI: https://doi.org/10.1097/GIM.0b013e3181c20bb3.

Hodgkinson, K.A., Connors SP, Merner N, et al. (2013). The natural history of a genetic subtype of arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L mutation in *TMEM43*. *Clinical Genetics, 83*, 4, 321-33. doi: 10.1111/j.1399-0004.2012.01919.x.

Hodgkinson K., Howes A.J., Boland P., et al. (2016). Long Term Clinical Outcome of Arrhythmogenic Right Ventricular Cardiomyopathy in Individuals with a p.S358L

Mutation in *TMEM43* Following Implantable Cardioverter Defibrillator Therapy. *Circulation: Arrhythmia and Electrophysiology, 9*, 3, e003589. https://doi.org/10.1161/CIRCEP.115.003589.

Hoogwegt M.T., Kupper N., Theuns D., et al. (2012). Undertreatment of anxiety and depression in patients with an implantable cardioverter-defibrillator: Impact on health status. *Health Psychology, 31*, 6, 745-753. doi:10.1037/a0028018.

Ingles J., Sarina T., Kasparian N., & Semsarian C. (2013). Psychological wellbeing and posttraumatic stress associated with implantable cardioverter defibrillator therapy in young adults with genetic heart disease. *International Journal of Cardiology, 168*, 4, 3779-3784 (2013). doi: 10.1016/j.ijcard.2013.06.006.

Jacq F., Foulldrin G., Savoure A., et al. (2009). A comparison of anxiety, depression and quality of life between device shock and nonshock groups in implantable cardioverter defibrillator recipients. *General Hospital Psychiatry, 31*, 3, 266-73. DOI: 10.1016/j.genhosppsych.2009.01.003.

James C.A., Tichnell C., Murray B., Daly A., Sears S.F., Calkins H. (2012). General and disease-specific psychosocial adjustment in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy with implantable cardioverter defibrillators: A large cohort study. *Circulation and Cardiovascular Genetics, 5*, 1, 18-24. doi: 10.1161/CIRCGENETICS.111.960898. PMID: 22238189.

Kapa S., Rotondi-Trevisan D., Mariano Z., et al. (2010). Psychopathology in patients with ICDs over time: Results of a prospective study. *Pacing and Clinical Electrophysiology, 33*, 2,

198-208. DOI: 10.1111/j.1540-8159.2009.02599.x.

Karatzias T., & Chouliara Z. (2009). Cognitive appraisals and physical health in people with posttraumatic stress disorder (PTSD). *Medical Hypotheses, 72*, 4, 444-7. DOI: 10.1016/j.mehy.2008.10.026.

Katritsis D.G. & Josephson M.E. (2012). Sudden cardiac death and implantable cardioverter defibrillators: Two modern epidemics? *Europace, 14,* 6, 787-94. DOI: 10.1093/europace/eus001.

Keren R., Aarons D., & Veltri E.P. (1991). Anxiety and depression in patients with life-threatening ventricular arrhythmias: Impact of the implantable cardioverter-defibrillator. *Pacing and Clinical Electrophysiology, 14*, 1, 181-7. DOI: 10.1111/j.1540-8159.1991.tb05088.x.

Kikkenborg Berg S., Thygesen L.C., Svendsen J.H. (2014). Anxiety predicts mortality in ICD patients: results from the cross-sectional national CopenHeartICDSurvey with register follow-up. *Pacing and Clinical Electrophysiology, 37*, 12, 1641. https://doi.org/10.1111/pace.12490.

Kroenke K., Spitzer R., & Williams J. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine, 16*, 9, 606-613. doi:10.1046/j.1525-1497.2001.016009606.x.

Ladwig K.H., Baumert J., Marten-Mittag B., et al. (2008). Posttraumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: Results from the prospective living with an implanted cardioverter-defibrillator study. *Archives of*

General Psychiatry, 65, 11, 1324-30. DOI: 10.1001/archpsyc.65.11.1324.

Lemon J. & Edelman S. (2007). Psychological adaptation to ICDs and the influence of anxiety sensitivity. *Psychology and Health Medicine, 12*, 2, 163-71. DOI: 10.1080/13548500500448478.

Leosdottir M., Sigurdsson E., Reimarsdottir G., et al. (2006). Health-related quality of life of patients with implantable cardioverter defibrillators compared with that of pacemaker recipients. *Europace, 8*, 3, 168-174. DOI: 10.1093/europace/euj052.

Levine, E. (2019, April 18). Classifications of Antiarrhythmic Agents. eMedicine. Retrieved 2/20/2020 from http://emedicine.medscape.com.

Liu T., Pursnani A., Sharma U.C., et al. (2014). Effect of the 2010 task force criteria on reclassification of cardiovascular magnetic resonance criteria for arrhythmogenic right ventricular cardiomyopathy. *Journal of Cardiovascular Magnetic Resonance, 16*, 1, 47. doi: 10.1186/1532-429X-16-47.

Magyar-Russell G., Thombs B.D., Cai J.X., et al. (2011). The prevalence of anxiety and depression in adults with implantable cardioverter defibrillators: A systematic review. *Journal of Psychosomatic Research, 71*, 4, 223-31. DOI: 10.1016/j.jpsychores. 2011.02.014.

Maia A.C.C.O., Braga A.A., Soares-Filho G., et al. (2014). Efficacy of cognitive behavioral therapy in reducing psychiatric symptoms in patients with implantable cardioverter defibrillator: An integrative review. *Brazilian Journal of Medicine and Biological Research, 47*, 4, 265-72. DOI: 10.1590/1414-431X20133418.

Marcus F., Edson S., & Towbin J. (2013). Genetics of Arrythmogenic Right Ventricular Cardiomyopathy: A Practical Guide for Physicians. *Journal of the American College of Cardiology, 61*, 19, 1945-1948. https://doi.org/10.1016/j.jacc.2013.01.073.

Maron B.J., Spirito P., Shen W.K., et al. (2007). Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Journal of the American Medical Association, 298*, 4, 405-12. DOI: 10.1001/jama.298.4.405.

Marshall WH., Furey M., Larsen B., et al. (1988). Right ventricular cardiomyopathy and sudden death in young people [correspondence]. *New England Journal of Medicine,* 319, 174-175. DOI: 10.1056/NEJM198807213190312.

Marshall P., Ketchell A., & Maclean J. (2012). Comparison of male and female psychological outcomes related to implantable cardioverter defibrillators (COMFORTID). *European Journal of Cardiovascular Nursing, 11*, 3, 313-21. DOI: 10.1016/j.ejcnurse.2011.06.010.

Matlock D.D., Peterson P.N., Heidenreich P.A., et al. (2011). Regional variation in the use of implantable cardioverter-defibrillators for primary prevention results from the national cardiovascular data registry. *Circulation and Cardiovascular Quality Outcomes, 4,* 1, 114-21. DOI: 10.1161/CIRCOUTCOMES.110.958264.

Mauro A.M.P. (2010). Long-term follow-up study of uncertainty and psychological adjustment among implantable cardioverter defibrillator recipients. *International Journal of Nursing Studies, 47*, 9, 1080-1088. doi: https://doi.org/10.1016/j.ijnurstu.2010.02.003.

Merner N.D., Hodgkinson, K.A., Haywood A.F., et al. (2008). Arrhythmogenic right ventricular

cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the *TMEM43* gene. *American Journal of Human Genetics, 82*, 4, 809-821. doi:10.1016/j.ajhg.2008.01.010.

Milting H., Klauke B., Christensen A.H., et al. (2015). The *TMEM43* Newfoundland mutation p.S358L causing ARVC-5 was imported from Europe and increases the stiffness of the cell nucleus. *European Heart Journal, 36*, 14, 872-881. https://doi-org.qe2a-proxy.mun.ca/10.1093/eurheartj/ehu077.

Morris P.L., Badger J., Chmielewski C., Berger E., & Goldberg R.J. (1991). Psychiatric morbidity following implantation of the automatic implantable cardioverter defibrillator. *Psychosomatics, 32*, 1, 58-64. DOI: 10.1016/S0033-3182(91)72112-9.

Ogrodniczuk J., Oliffe J., Kuhl D., & Gross P.A. (2016). Men's mental health: Spaces and places that work for men. *Canadian Family Physician, 62*, 6, 463-4. PMCID: PMC4907547.

Ohno S. (2016). The genetic background of arrhythmogenic right ventricular cardiomyopathy. *Journal of Arrhythmias, 32*, 5, 398-403. doi: 10.1016/j.joa.2016.01.006.

Online Mendelian Inheritance in Man, OMIM®.Johns Hopkins University (Baltimore, MD). MIM Number: [604400]: [12/02/2013]: World Wide Web URL: https://omim.org/

Online Mendelian Inheritance in Man, OMIM®.McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), July 8, 2020. World Wide Web URL: https://omim.org/.

Pallant, J. (2005). SPSS Survival Manual: A step by step guide to data analysis using SPSS for Windows (Version 12; 2nd edition). Allen & Unwin. National Library of Australia.

Passman R., Subacius H., Ruo B., et al. (2007). Implantable cardioverter defibrillators and quality of life: results from the defibrillators in nonischemic cardiomyopathy treat ment evaluation study. *Archives of Internal Medicine, 167*, 20, 2226-32. DOI: 10.1001/archinte.167.20.2226.

Paulin F.L., Hodgkinson K.A., MacLaughlan S., et al. (2020). Exercise and Arrhythmic Risk in *TMEM43* p.S358L Arrhythmogenic Right Ventricular Cardiomyopathy. *Heart Rhythm, S1547-5271*, 20, 30181-8.

Pearson C., Janz T., & Ali J. (2013). Mental Health and Substance Use disorder in Canada: Health at a Glance. Statistics Canada catalogue no.82-624x.

Pedersen S.S., Van den Berg M., Erdman R.A.M., et al. (2009). Increased anxiety in partners of patients with a cardioverter-defibrillator: The role of indication for ICD therapy, shocks, and personality. *Pacing and Clinical Electrophysiology, 32*, 2, 184-192 (2009). doi: 10.1111/j.1540-8159.2008.02201.x.

Pilichou K., Thiene G., Bauce B., et al. (2016). Arrhythmogenic cardiomyopathy. *Orphanet Journal of Rare Disorders,* 11, 33. doi: 10.1186/s13023-016-0407-1.

Piotrowicz K., Noyes K., Lyness J.M., et al. (2007). Physical functioning and mental well-being in association with health outcome in patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial II. *European Heart Journal, 28*, 5, 601-7. DOI: 10.1093/eurheartj/ehl485.

Rahmawati A., Chishaki A., Sawatari H., et al. (2013). Gender disparities in quality of life and psychological disturbance in patients with implantable cardioverter-defibrillators.

Circulation Journal, 77, 5, 1158-1165. PMID: 23337265.

Ramasubbu R., Beaulieu S., Taylor V.H., et al. (2012). The CANMAT Task Force recommendations for the management of patients with mood disorders and comorbid medical conditions: Diagnostic, assessment, and treatment principles. *Annals of Clinical Psychiatry, 24*, 1, 82-90. PMID: 22303524.

Read A., & Donnai D. (2015). *New Clinical Genetics (3rd edition)*. Banbury, UK: Scion.

Redhead A.P., Turkington D., Rao S., Tynan M.M., & Bourke J.P. (2010). Psychopathology in postinfarction patients implanted with cardioverter-defibrillators for secondary prevention. A cross-sectional, case-controlled study. *Journal of Psychosomatic Research, 69*, 6, 555-63. DOI: 10.1016/j.jpsychores.2010.06.002.

Rhodes A.C., Murray B., Tichnell C.,et al. (2017). Quality of life metrics in arrhythmogenic right ventricular cardiomyopathy patients: The impact of age, shock and sex. *International Journal of Cardiology, 248*, 1, 216-220 (2017). DOI: 10.1016/j.ijcard.2017.08.026.

Romero J., Mejia-Lopez E., Manrique C., & Lucariello R. (2013). Arrythymogenic Right Ventricular Cardiomyopathy (ARVC/D): A Systematic Literature Review. *Clinical Medicine Insights Cardiology,* 7, 97-114. doi: 10.4137/CMC.S10940.

Roston T.M., Krahn A.D., Ong K., & Sanatani S. (2019). The merits of the ICD for inherited heart rhythm disorders: A critical re-appraisal. *Trends in Cardiovascular Medicine, S1050-1738,* 19, 30143-4. DOI: 10.1016/j.tcm.2019.10.004.

Rottmann N., Skov O., Andersen C.M., Theuns D.A.M.J., & Pedersen S.S. (2018). Psychological distress in patients with an implantable cardioverter defibrillator and their partners.

Journal of Psychosomatic Research, 113, 16-21. https://doi.org/10.1016/j.jpsychores.2018.07.010.

Sattar Y., Abdullah H.F., Samani E.N., Myla M., & Ullah W. (2019). Arrythmogenic Right Ventricular Cardiomyopathy/Dysplasia: An Updated Review of Diagnosis and Management. *Cureus, 11*, 8, e5381. doi: 10.7759/cureus.5381.

Sears S.F. & Conti J.B. (2006). Psychological aspects of cardiac devices and recalls in patients with implantable cardioverter defibrillators. *American Journal of Cardiology, 98*, 4, 565-7. DOI: 10.1016/j.amjcard.2006.02.066.

Sears S.F., Vazquez Sowell L.D., Kuhl E.A., et al. (2007). The ICD shock and stress management program: A randomized trial of psychosocial treatment to optimize quality of life in ICD patients. *Pacing and Clinical Electrophysiology*, *30,* 7, 858-64. DOI: 10.1111/j. 1540-8159.2007.00773.x.

Schaffer A., McIntosh D., Goldstein B.I., et al. (2012). The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders (Review Article). *Annals of Clinical Psychiatry, 24*, 1, 6-22. PMID: 22303519.

Schulz S.M., Massa C., Grzbiela A., et al. (2013). Implantable cardioverter defibrillator shocks are prospective predictors of anxiety. *Heart Lung, 42*, 2, 105-11. DOI: 10.1016/j.hrtlng. 2012.08.006.

Schwartz P.J., Spazzolini C., Priori S.G., et al. (2010). Who are the long-QT syndrome patients who receive an implantable cardioverter-defibrillator and what happens to them?: Data

from the European Long-QT Syndrome implantable cardioverter-defibrillator (LQTS ICD) registry. *Circulation, 122*, 13, 1272-82. DOI: 10.1161/CIRCULATIONAHA. 110.950147.

Sears S.F., & Kirian K. (2010). Shock and patient-centered outcomes research: is an ICD shock still a critical event? *Pacing and Clinical Electrophysiology, 33*, 1437-1441. https://doi.org/10.1111/j.1540-8159.2010.02872.x.

Silvano M., Mastella G., Zorzi A., et al. (2016). Management of Arrhythmogenic right ventricular cardiomyopathy. *Minerva Medica, 107*, 4, 194-216.

Stafford L., Berk M., & Jackson H.J. (2007). Validity of the Hospital Anxiety and Depression scale and Patient Health Questionnaire-9 to screen for depression in patients with coronary artery disease. *General Hospital Psychiatry, 29*, 5, 417-424. DOI: 10.1016/ j.genhosppsych.2007.06.005.

Sumner JA., Kronish IM., Pietrzak RH., Shimbo D., et al. (2015). Dimensional structure and cor relates of posttraumatic stress symptoms following suspected acute coronary syndrome. Journal of Affective Disorders, 186, 178-185. doi: 10.1016/j.jad.2015.06.013.

Statistics Canada. Table 13-10-0465-01 Mental health indicators. https://doi.org/10.25318/1310046501-eng. Retrieved 02-23-2020.

Teare M.D. (2011). Candidate gene association studies. *Methods in Molecular Biology,* 713, 105-17. DOI: 10.1007/978-1-60327-416-6_8.

Thomas S.A., Friedmann E., Gottlieb S.S., et al. (2009). Changes in psychosocial distress in outpatients with heart failure with implantable cardioverter defibrillators. *Heart Lung, 38*,

2, 109-20. DOI: 10.1016/j.hrtlng.2008.05.005.

Thylén I., Moser D.K., Strömberg A., et al. (2016). Concerns about implantable cardioverter-defibrillator shocks mediate the relationship between actual shocks and psychological distress. *Europace, 18*, 6, 828-835. doi: 10.1093/europace/euv220.

Tomitaka S., Kawasaki Y., Ide K., et al. (2018). Distributional patterns of item responses and total scores on the PHQ-9 in the general population: Data from the National Health and Nutrition Examination Survey. *BMC Psychiatry, 18*, 1, 108. DOI: 10.1186/s12888-018-1696-9.

Tomitaka S., Kawasaki Y., Ide K., et al. (2018). Stability of the distribution of Patient Health Questionnaire-9 scores against age in the general population: Data from the National Health and Nutrition Examination Survey. *Frontiers in Psychiatry, 9*, 390. DOI: 10.3389/fpsyt.2018.00390.

Towbin J., McKenna W., Abrams D., et al. (2019) 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy: Executive Summary. *Heart Rhythm, 16*, 11, e373-e407. https://doi.org/10.1016/j.hrthm.2019.09.019.

United States Department of Veteran Affairs National Center for Posttraumatic Stress Disorder: Advancing science and promoting understanding of traumatic stress using the PTSD checklist (PCL). (2012). https://sph.umd.edu/sites/default/files/files/PTSDChecklistScoring.pdf.

van den Berk-Clark C., Secrest S., Walls J., et al. (2018). Association between posttraumatic

stress disorder and lack of exercise, poor diet, obesity, and co-occurring smoking: A sys tematic review and meta-analysis. *Health Psychology, 37*, 5, 407-416. DOI: 10.1037/ hea0000593.

Van den Broek K.C., Nyklicek I., Van der Voort P.H., Alings M., & Denollet J. (2008). Shocks, personality, and anxiety in patients with an implantable defibrillator. *Pacing and Clinical Electrophysiology, 31*, 7, 850-7. DOI: 10.1111/j.1540-8159.2008.01099.x.

Van den Broek K.C., Heijmans N., & Van Assen M. (2013). Anxiety and depression in patients with an implantable cardioverter defibrillator and their partners: A longitudinal study. *Pacing and Clinical Electrophysiology, 36*, 3, 362-371. doi: 10.1111/pace.12055.

Vasquez L.D., Kuhl E.A., Shea J.B., et al. (2008). Age-specific differences in women with implantable cardioverter defibrillators: An international multi center study. *Pacing and Clinical Electrophysiology, 31*, 12, 1528–34. DOI: 10.1111/j.1540-8159.2008.01223.x.

Vasquez L.D., Conti J.B., & Sears S.F. (2010). Female-specific education, management, and lifestyle enhancement for implantable cardioverter defibrillator patients: The FEMALE-ICD Study. *Pacing and Clinical Electrophysiology, 33*, 9, 1131-40. DOI: 10.1111/j. 1540-8159.2010.02787.x.

Versteeg H., Timmermans I., Meine M., et al. (2017). Prevalence and risk markers of early psychological distress after ICD implantation in the European REMOTE-CIED study cohort. *International Journal of Cardiology,* 240, 208-213. doi: 10.1016/j.ijcard. 2017.03.124.

von Kanel R., Baumert J., Kolb C., Cho E.Y.N., & Ladwig K.H. (2011). Chronic posttraumatic stress and its predictors in patients living with an implantable cardioverter defibrillator. *Journal of Affective Disorders, 131*, 1-3, 344-52. DOI: 10.1016/j.jad.2010.12.002.

Wang L., Lu K., Li J., et al. (2015). [Value of Patient Health Questionnaires (PHQ)-9 and PHQ-2 for screening depression disorders in cardiovascular outpatients]. *Zhonghua Xin Xu Gu Bing Za Zhi, 43*, 5, 428-31. PMID: 26419989.

Watkins H., Ashrafian B.M., & Redwood C. (2011). Inherited Cardiomyopathies. *New England Journal of Medicine, 364*, 1643-1656. DOI: 10.1056/NEJMra0902923.

Weathers, Litz, Huska, & Keane. National Center for PTSD-Behavioral Science Div. United States Department of Veteran Affairs National Center for Posttraumatic Stress Disorder: Advancing science and promoting understanding of traumatic stress using the PTSD checklist (PCL). (2012). https://www.bu.edu/wheelock/files/2018/05/PTSD-checklist-Adult.pdf.

Webster G., Panek K., Labella M., et al. (2014). Psychiatric functioning and quality of life in young patients with cardiac rhythm devices. *Pediatrics, 133*, 4, e964-72. doi: 10.1542/peds.2013-1394.

Wilkins K., Lang A., & Norman S. (2011). Synthesis of the psychometric properties of the PTSD checklist (PCL) Military, Civilians, and specific versions. *Depression and Anxiety, 28*, 7, 596-606.

Winkel B.G. & Tfelt-Hansen J. (2019). Editorial Commentary: When should the patient with an inherited cardiac disease have an ICD? *Trends in Cardiovascular Medicine, S1050-1738*,

19, 30154-9. DOI: 10.1016/j.tcm.2019.11.004.

Xue Y., Taub P.R., Iqbal N., et al. (2012). Cardiac biomarkers, mortality, and post-traumatic stress disorder in military veterans. *American Journal of Cardiology, 109*, 8, 1215-8. DOI: 10.1016/j.amjcard.2011.11.063.

Zung W.W.K. (1971). A rating instrument for anxiety disorders. *Psychosomatics,12*, 6, 371-9. PMID 5172928.

Zung W.W. (1974). The measurement of effects: Depression and Anxiety. *Modern Problems in Pharmacopsychiatry, 7*, 0, 170-88. PMID 4153516.

APPENDIX A

ETHICS APPROVAL

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

July 14, 2017

Faculty of Medicine
Disciple of Medicine

Dear Dr. Orzylowski:

Researcher Portal File # 20171983
Reference # 2017.071

RE: "Living with a genetic form of arrhythmogenic right ventricular cardiomyopathy (ARVC) causing sudden cardiac death (SCD) in the family: anxiety, depression, and post traumatic stress disorder (PTSD) in (a) affected family members with an implantable cardioverter defibrillator (ICD), (b) unaffected siblings of those with an ICD born at a 50% risk of having the disease, but shown to be mutation negative and (c) spouses of affected family members with an ICD."

This will acknowledge receipt of your correspondence.

This correspondence has been reviewed by the Chair under the direction of the Health Research Ethics Board (HREB). ***Full board approval*** of this research study is granted for one year effective **May 11, 2017**.

This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- Cover letter and consent for spouses, approved
- ICD positive cover letter and consent, approved
- Negative Siblings letter and consent, approved
- Zung Self-Rating Anxiety Scale, approved
- Telephone script, approved
- Support information for patients, approved
- Initial contact telephone Script for the Negative Siblings, approved
- PTSD Checklist-Civilian Form (PCL-C), approved
- Patient Health Questionnaire – 9, approved

APPENDIX B

COVER LETTER AND CONSENT

Date:

You are invited to take part in a research study called:

Living with a genetic form of arrhythmogenic right ventricular cardiomyopathy (ARVC) causing sudden cardiac death (SCD) in the family: anxiety, depression, and post traumatic stress disorder (PTSD) in (a) affected family members with an implantable cardioverter defibrillator (ICD), (b) unaffected siblings of those with an ICD born at a 50% risk of having the disease, but shown to be mutation negative and (c) spouses of affected family members with an ICD.

You are being invited to take part in this study as a person who has been tested for the p.S358L mutation causing ARVC **, who had the mutation and now has an Implantable cardioverter defibrillator (ICD)** .

We would like to know how the ARVC diagnosis in your family has affected/impacted your mental well being. Ultimately, we hope to find information that may improve mental health services available to families with ARVC.

We have three short questionnaires that ask you questions about how you feel.

Filling out these questionnaires is voluntary and you are free to leave out any question you do not wish to answer.

You do not have to take part.

Taking part will not affect any healthcare you or your family receives.

Your name will never be reported in any papers or reports prepared from the research.

The data we collect for this study will be stored for at least 5 years. The questionnaires will be coded and linked with data from a previous study on ARVC that you participated in (HREB 00-176 SCD Cardiomyopathy).

Should you wish to withdraw from the study at any time, any data you have provided will be removed from the data set and destroyed.

Fillings out the three surveys should take approximately 15 minutes. Please return it in the postage-paid envelope provided. If you have any questions or concerns about the study or would like more information, please feel free to contact the following individuals:

Dr. Holly Etchegary, Assistant Professor, Faculty of Medicine
Phone: 709-864-6605; Email: holly.etchegary@med.mun.ca

Dr. Kathy Hodgkinson, Associate Professor, Faculty of Medicine
Phone: 709-864-6694; Email: khodgkinson@mun.ca

Dr. Magda Orzylowski : M. Sc Candidate Clinical Epidemiology, Faculty of Medicine
Memorial University of Newfoundland
Email: mo3633@mun.ca

Or you can talk to someone who is not involved with the study at all, but can advise you on your rights as a participant in a research study. This person can be reached through:

Ethics Office at 709-777-6974
Email at info@hrea.ca

This study has been reviewed and given ethics approval by the Newfoundland and Labrador Health Research Ethics Board.

We thank you for taking the time to give us your thoughts and opinions.

Sincerely,

Drs. Holly Etchegary, Kathy Hodgkinson, and Magda Orzylowski on behalf of the research team

CONSENT TO TAKE PART IN RESEARCH

Name of Principal Investigator: Magdalena Orzylowski, MD.

Supervisor of Principal Investigator: Dr. Kathleen Hodgkinson

Location: Department of Clinical Epidemiology, Memorial University, St. John's, Newfoundland

TITLE: Psychiatric comorbidity in young adults with a genetic subtype of Arrhythmogenic Right Ventricular Cardiomyopathy and implantable cardiac defibrillators

INVESTIGATORS: Dr. Magdalena Orzylowski, Dr. Kathy Hodgkinson

You have been invited to take part in a research study. Taking part in this study is voluntary. You decide whether you want to participate in this study. If you decide to take part, you are free to leave the study at any time. This will not affect your current health care management.

Before you decide, you need to understand what the study is about, and what risks and benefits come with it if you decide to take part. This consent form will explain the study. Once you read this consent form, you are free to contact the research team with further questions or concerns (contact information provided at end of consent form).

Please read this carefully. Take your time. Mark anything you don't understand or want to ask questions about.

When you have read the study, the research team will:

-Discuss the study with you and answer any questions or concerns if needed.

-Keep any information you provide confidential

-Be available throughout the study for any concerns or questions

1. INTRODUCTION

Individuals with identified genetic heart disease face unique challenges as well as their unaffected family members. Those who have received implantable cardiac defibrillators (ICD's) may face further more difficulties adjusting to this life change, despite the fact that the ICD is the best treatment choice.

Individuals with genetic heart disease are followed closely by different doctors and health teams. However, despite all of the stress surrounding this health condition, the psychological wellbeing of these individuals has not been properly assessed and followed up. It would be important to take a look at this in case certain individuals could benefit from mental health services such as counselling, psychology, supportive groups, or psychiatry.

2. PURPOSE OF THE STUDY:

The purpose of this study is to gather information via questionnaires to determine if there are any concerns about depression, anxiety, or posttraumatic stress symptoms in this group.

3. DESCRIPTION OF STUDY PROCEDURES

After you have spoken to Dr. Kathy Hodgkinson and filled out the consent to participate in the

study (part of the mailed package) you would be expected to fill out the accompanied questionnaires also inside the package mailed to you. Once you have completed the form and the questionnaires, we ask that you put the documents back in the package and place the return postage stamp and address on the package to send back to us (at no cost to you). After we have received your returned package, we will contact you for any questions or concerns that we may have, and to ask you if you had any as well. After this follow up phone call, you have finished the study.

4. LENGTH OF TIME

This study will last approximately 2 months. Once you complete the forms and scales in the administered package, the research team will follow up with you regarding any concerns or questions that you or they may have. After this, the study is concluded. The research team may make suggestions or recommendations about further mental health services or care to you, but this will be your choice, and is not part of the research project itself.

5. POSSIBLE RISKS AND DISCOMFORTS

You must consent to this study in order to participate. All research may have some risks and discomforts associated with it. In our study, we will be calling you on at least one occasion which may take up several minutes of your time. We are also sending you a package with 3 different questionnaires and a consent form to read and sign (this form) which also takes some time to read through. Some people may find that they have some trouble answering some of the questions in the questionnaires because they upset them or they feel they may be too personal. These questionnaires ask you about your mental wellbeing and we hope that you will answer them as honestly as possible for us to get a good understanding of how you are doing. If you find that it is too difficult to fill out the questionnaires, or you have specific questions about them, please feel free to give us a call and we can help you through it. We are available to talk about any questions or concerns you may have.

6. BENEFITS

By participating in this study, we hope that it can benefit you. Learning more about you through the information we gather can help us with your health care needs. We want to make sure that you are physically and mentally well. We want to provide you the best health care possible and provide you with services that you may not know about or may have not used up to this point. If we feel that you would benefit from further mental health follow after the study is finished, we will contact you and tell you about all of the options available to you. Your wellbeing is most important to us.

When you are ready to mail back your research packages, we will provide return postage. There will be no cost to you to participate in this study.

7. LIABILITY STATEMENT

Signing this form gives us your consent to be in this study. When you sign this form, you do not give up your legal rights. Researchers or agencies involved in this research study still have their legal and professional responsibilities to you.

8. PRIVACY AND CONFIDENTIALITY

Protecting your privacy is important to us. Every effort is made to protect your privacy. How

ever, we cannot completely guarantee this. There are some specific examples in which we may have to break confidentiality. These exceptions are no different than when you are in hospital for non-research reasons. We may have to break confidentiality if we feel that you are in danger to yourself, others, or if a child is in danger. We may also have to break confidentiality if it is required by law. A copy of this consent will be put in your health records.

When you sign this consent form you give us permission to:

1. Collect information from you
2. Collect information from your health record
3. Share information with the people conducting the study
4. Share information with the people responsible for protecting your safety. This may also include a substitute decision maker if you have one.

Access to medical records

The members of the research team will see health and study records that identify you by name or MCP numbers. The research ethics board may need to look at your health records when supervised by the research team. You can ask for a list of the people who will have access to this information.

Use of your study information

The research team will collect and use only the information they need for the purpose of this study. This information includes:

- ➢ Date of birth
- ➢ Sex
- ➢ Medical diagnoses and history
- ➢ Psychiatric diagnoses
- ➢ Medications
- ➢ Information from study questionnaires

We hope that with the research results we will be able to publish the study and present it at the Memorial University Research Day in the Department of Psychiatry.

We will protect your privacy and confidentiality by using only password protected usb devices and computer storage. Any health records that are stored in paper format will be kept under lock and key in the Department of Clinical Epidemiology under the supervision of Dr. Kathy Hodgkinson.

Access to your records: You may ask the researcher to see the information that has been collected about you.

9. QUESTIONS OR CONCERNS

You will have phone contact with the investigator (and possibly meet with the investigator or supervisor of the project if time and location permits) to further discuss the study and this

consent form if you would like. Please feel free to bring up any questions or concerns. The investigator at the St. John's site is Dr. Magdalena Orzylowski. The supervisor (also at the St. John's site) is Dr. Kathy Hodgkinson.

Contact information of Principal Investigator:

Magda Orzylowski, 4th year Psychiatry Resident, Department of Psychiatry, Memorial University

Mo3633@mun.ca, pager number # 758-9028

Contact information of Investigator Supervisor:

Dr. Kathy Hodgkinson, Assistant Professor, Department of Clinical Epidemiology, Memorial University

khodgkin@mun.ca, Telephone #709-864-6694

You can also talk to someone at the Ethics Office. The ethics office is not directly involved in the study, but they can advise you on your rights as a participant in a research study. Their contact information:

Health Ethics Research Board, Ethics Officer

info@hrea.ca, Telephone #709-770-8905

10. DECLARATION OF FINANCIAL INTEREST

No financial support has been provided for this project. If this changes, you will be notified.

After you have signed this consent, you will be given a copy by mail.

After you have read the above and agree to participate, please sign and date below and mail back with completed package as indicated on return postage.

Date _____

Full name _____

Signature _____

Thank you for taking the time to read this! We really appreciate it!

APPENDIX C

PSYCHOMETRIC SCALES

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING: 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

NAME _____ DATE _____

Zung Anxiety Self-Assessment Scale

	None or a little of the time	Some of the time	Good part of the time	Most or all of the time
1. I feel more nervous and anxious than usual	1	2	3	4
2. I feel afraid for no reason at all	1	2	3	4
3. I get upset easily or feel panicky	1	2	3	4
4. I feel like I'm falling apart and going to pieces	1	2	3	4
5. I feel that everything is all right and nothing bad will happen	4	3	2	1
6. My arms and legs shake and tremble	1	2	3	4
7. I am bothered by headaches, neck and back pains	1	2	3	4
8. I feel weak and get tired easily	1	2	3	4
9. I feel calm and and can sit still easily	4	3	2	1
10. I can feel my heart beating fast	1	2	3	4
11. I am bothered by dizzy spells	1	2	3	4
12. I have fainting spells or feel faint	1	2	3	4
13. I can breath in and out easily	4	3	2	1
14. I get feelings of numbness and tingling in my fingers and toes	1	2	3	4
15. I am bothered by stomachaches or indigestion	1	2	3	4
16. I have to empty my bladder often	1	2	3	4
17. My hands are usually dry and warm	4	3	2	1
18. My face gets hot and blushes	1	2	3	4
19. I fall asleep easily and get a good night's rest	4	3	2	1
20. I have nightmares	1	2	3	4

Converting Raw Score Total to Anxiety Index

RAW SCORE	ANXIETY INDEX	RAW SCORE	ANXIETY INDEX	RAW SCORE	ANXIETY INDEX
20	25	40	50	60	75
21	26	41	51	61	76
22	28	42	53	62	78
23	29	43	54	63	79
24	30	44	55	64	80
25	31	45	56	65	81
26	33	46	58	66	83
27	34	47	59	67	84
28	35	48	60	68	85
29	36	49	61	69	86
30	38	50	63	70	88
31	39	51	64	71	89
32	40	52	65	72	90
33	41	53	66	73	91
34	43	54	68	74	93
35	44	55	69	75	94
36	45	56	70	76	95
37	46	57	71	77	96
38	48	58	73	78	98
39	49	59	74	79	99
				80	100

Raw Score Total ☐ Anxiety Index ☐

Interpreting the Anxiety Index

Anxiety Index	Clinical Interpretation
Below 45	Within normal range
45 – 59	Minimal to moderate anxiety
60 – 74	Marked to severe anxiety
75 and over	Most extreme anxiety

- Check that all statements have been answered
- Scoring values are printed next to the response
- Add up the Raw Total Score
- Convert the Raw Total to the Anxiety Index

Instruction for use: (Zung Anxiety Assessment Tool)

1. The same caregiver should administer this test each time.
2. Choose a quiet place, preferably the same location each time the test is administered.
3. The administration of this test should not be immediately after some mental trauma or anxiously period.
4. Speak in a soft, pleasant tone.
5. Answer all questions by placing a check in the box to the left of the number under the appropriate answer.
6. Add the Raw Score values (numbers to the right of the check) for all questions and record the total in the "RAW SCORE TOTAL" box.
7. Compare the raw score to the anxiety index on the conversion chart and record the corresponding anxiety index in the "ANXIETY INDEX" box.
8. Compare the anxiety index with the clinical interpretation chart.

Consult Pharm 1996; 11 (Suppl 4)

PTSD Checklist (PCL)

Patient Name: _____ **Date:** _____

If an event listed on the Life Events Checklist **happened to you** or you **witnessed it,** please complete the items below. If more than one event happened, please choose the one that is **most troublesome to you now.**

The event you **experienced** was _____ (EVENT) on _____ (DATE).

Instructions: Below is a list of problems and complaints that people sometimes have in response to stressful life experiences. Please read each one carefully, then **circle** one of the numbers to the right to indicate how much you have been **bothered** by the problem **in the past month.**

BOTHERED BY	NOT AT ALL	A LITTLE BIT	MODERATELY	QUITE A BIT	EXTREMELY
1. Repeated disturbing memories, thoughts, or images of the stressful experience?	1	2	3	4	5
2. Repeated, disturbing dreams of the stressful experience?	1	2	3	4	5
3. Suddenly acting or feeling as if the stressful experience were happening again (as if you were reliving it)?	1	2	3	4	5
4. Feeling very upset when something reminded you of the stressful experience?	1	2	3	4	5
5. Having physical reactions (e.g., heart pounding, trouble breathing, or sweating) when something reminded you of the stressful experience?	1	2	3	4	5
6. Avoiding thinking about or talking about the stressful experience or avoiding having feelings related to it?	1	2	3	4	5
7. Avoiding activities or situations because they remind you of the stressful experience?	1	2	3	4	5
8. Trouble remembering important parts of the stressful experience?	1	2	3	4	5
9. Loss of interest in activities that you used to enjoy?	1	2	3	4	5
10. Feeling distant or cut off from other people?	1	2	3	4	5
11. Feeling emotionally numb or being unable to have loving feelings for those close to you?	1	2	3	4	5
12. Feeling as if your future will somehow be cut short?	1	2	3	4	5
13. Trouble falling or staying asleep?	1	2	3	4	5
14. Feeling irritable or having angry outbursts?	1	2	3	4	5
15. Having difficulty concentrating?	1	2	3	4	5
16. Being "super alert" or watchful or on guard?	1	2	3	4	5
17. Feeling jumpy or easily startled?	1	2	3	4	5

APPENDIX D

TELEPHONE SCRIPT FOR ICD PATIENTS

Telephone Script for ICD

Telephone Script for Dr. Kathy Hodgkinson (or one of the genetic counsellors with more recent contact : Ashley Collier, Sarah Predham or Fiona Curtis)

The above named individuals know the affected ICD patients and their families well. The only ICD patients we will contact are those who actively follow witht eh ICD clinic at the Health Sciences Centre and participated in the large cardiomyopathy / SCD dataset (HREB 00-176).

The above named individuals will make initial contact with the ICD patients to inform them of the research study.

Hello, may I please speak to (insert name)?

When desired person is on the phone:

Hello [first name], this is XXXXX calling, how are you? I am calling to let you know about a new ARVC research project we are starting that might be of interest to you.

We want to ask about the psychological wellbeing of ICD patients like yourself. This is to try and understand how these issues might affect you.

This requires you to fill out three very short questionnaires, which I can mail out to you (with return postage).

There is certainly no requirement at all that you should take part. This study has nothing to do with the care you or your family receives from the cardiac clinic. But if you would like to know more about the study, would it be okay if one of the research team members involved in the study gives you a call? She can give you more detail about the surveys and mail them out to you.

If refusal: Okay, no problem. Thank you for taking the time to speak with me.

If yes: Okay, is there a time that works best for you? I will give Magda your telephone number and she will contact you. Thanks for your time, and good to speak with you again.

APPENDIX E

OTHER SUPPORTING DOCUMENTS

Support Information

Useful numbers for individuals taking part in the research project.

Mental Health Crisis Line
24 hour crisis support
1-888-737-4668

CHANNEL Warm Line
Non-judgemental telephone peer support
Available 11am to 11pm
1-855-753-2560

Dr. Kathy Hodgkinson
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Memorial University
khodgkin@mun.ca
709 864 6694

Dr. Holly Etchegary
Assistant Professor, Faculty of Medicine
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