HEART RHYTHM CHANGES IN EATING DISORDERS

by

Mikyla Janzen

B.Sc.H., Queen's University, 2014

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Experimental Medicine)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

July 2017

Abstract

Anorexia nervosa (AN) is a complex psychiatric disorder with the highest mortality rate of any eating disorder. A subset of these deaths may be sudden and attributed to cardiac rhythm changes which may be present during acute AN. Specifically, the repolarization phase of each heartbeat, as visualized by the QT interval on electrocardiogram (ECG), has been suggested as a potential prognostic tool. In addition, many AN patients are prescribed psychopharmacotherapy to treat concurrent depression and/or anxiety which may accentuate ECG changes.

Through four research studies, this thesis explored three hypotheses:

1. Comprehensive cardiac testing is an effective and cost-efficient means of evaluation.
2. Psychopharmacotherapy will alter the ECG in eating disorders
3. Cardiac repolarization in AN will differ from healthy controls at rest and during exercise.

In the first study, Hypothesis 1 was tested by means of a cost analysis of patients referred for inherited heart rhythm disorder evaluation. Analyses revealed multidisciplinary cardiac testing was effective and did not incur unreasonably high costs.

Secondly, a retrospective case-control ECG review was conducted to evaluate Hypotheses 2 and 3. The QT interval was not clinically different between eating disorder patients and healthy controls, but patients were more likely to show T-wave flattening or inversion on ECG, which have been previously associated with SUD risk.

Thirdly, Hypothesis 3 was further analyzed through a systematic review and meta-analysis of the current literature surrounding the resting QT interval in AN. Again, there was no difference in the QT interval, but AN patients had greater QT dispersion (interlead difference on ECG) compared to controls. QT dispersion has also been linked to increased SUD risk.

Finally, we are prospectively assessing the ECG during modified exercise in eating disorder patients to further explore Hypothesis 3. Preliminary data suggest QT dynamics as heartrate increases may be abnormal.

Overall, it appears that the resting QT interval may not be a direct marker of SUD risk in AN. However, more subtle markers of repolarization abnormality such as T-wave changes and

QT dispersion may be superior at rest. During exercise, QT interval dynamics may regain relevance in assessing SUD risk.

Lay Summary

Anorexia nervosa (AN) is a psychiatric disorder where individuals have extremely low body weight, are intensely afraid of gaining weight, and have a distorted body image. AN mostly affects adolescent females but is often a lifelong battle and has the highest mortality of any eating disorder. Some of these deaths may be caused by heart rhythm changes that can be seen before tragedy occurs; however, such changes have not been consistently reported in individuals with AN. The goal of this thesis was to improve our understanding of the heart rhythm changes that occur in anorexia nervosa at rest, during exercise, and throughout treatment. To do this, we analyzed the costs of similar heart conditions, reviewed the current research on the topic, and assessed local adolescent and adult patients. The results suggest that heart rhythm changes play a minor role in the small but concerning risk of death in AN.

Preface

The research conducted in this thesis was designed by the author (MJ) in conjunction with the supervisory committee (Drs. Shubhayan Sanatani and Pei-Yoong Lam) and supervisor (Dr. Andrew Krahn). In addition, Dr. Christopher Cheung played a significant role in the design of the studies presented in Chapters 2 and 3, and work by Dr. Gareth Padfield sparked the research questions regarding cardiac electrophysiology in the setting of eating disorders. The author (MJ) performed all prospective data collection and analyzed all data with the support of the supervisory committee and other collaborators.

A version of *Chapter 2 – Cost Analysis of Patients Referred for Evaluation of Inherited Heart Rhythm Disorder* was published in the Canadian Journal of Cardiology in 2016[1]. The author (MJ) was first author of this publication, completed all adult data collection, all analysis, and wrote the manuscript. Data from British Columbia Children's Hospital was collected by local Research Assistants, Taylor Cunningham and Frances Perry. This study was approved by the UBC Providence Healthcare Research Ethics Board, Certificate H15-03011.

Demographic data and clinical characteristics (i.e. laboratory measures) collected by Mackenzie Robertson and Katie Coopersmith were used in *Chapter 3 – Electrocardiographic Markers of Repolarization in Eating Disorders: a Case Control Study*. The authors plan to submit this study as a Research Letter to the *Journal of the American College of Cardiology*; as such, the chapter is formatted as an expanded abstract to meet publication requirements. This study was approved by UBC Providence Healthcare Research Ethics Board, Certificate H16-00060.

Dr. Navraj Malhi was a second reviewer of the collected data in *Chapter 4 – The QT Interval in Anorexia Nervosa: a Systematic Review and Meta-Analysis*. Guidance regarding review design and analyses was provided by Dr. Nathaniel Hawkins.

Research described in *Chapter 5 – Evaluation of the Exercise Electrocardiogram in Anorexia Nervosa* was approved by the UBC Providence Healthcare Research Ethics Board, Certificate H16-01420. Local clinical nurses, Ashley Beaulieu and Gabriela Cruz, assisted with patient recruitment coordination.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AAP	Atypical antipsychotic
AN	Anorexia nervosa
AN-R	Anorexia nervosa – restrictive subtype
AN-BP	Anorexia nervosa – binge/purge subtype
BCIAP	British Columbia Inherited Arrhythmia Program
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
CASPER	Cardiac Arrest Survivors with Preserved Ejection fraction Registry
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBW	Estimated body weight
ECG	Electrocardiogram
ED	Eating disorder
EDNOS	Eating disorder not otherwise specified
HR	Heart rate
HRV	Heart rate variability
ICD	Implantable cardioverter defibrillator
IHRD	Inherited heart rhythm disorder
IQR	Interquartile range
LQTS	Long QT syndrome
MSP	Medical services plan
OSFED	Other specified feeding and eating disorder
QTc	Corrected QT interval
UFED	Unspecified feeding and eating disorder
RFS	Refeeding syndrome
SCA	Sudden cardiac arrest
SMR	Standard mortality ratio
SSRI	Selective serotonin reuptake inhibitor
SUD	Sudden unexpected death

Acknowledgements

I am forever grateful to Dr. A. Krahn for his continued mentorship, support, and inspiration, from academic clinical curiosity to professional research conduct. Thank you to Karen Gibbs for her unwavering support, and my supervisory committee, Drs. Sanatani and Lam, for guiding me through this project.

Thank you to the UBC Faculty of Medicine for their financial support, and the Canadian Cardiovascular Society Academy for expanding my education at the 2016 Canadian Cardiovascular Congress through the Have a Heart Bursary program.

Special thanks to my parents for their support and love throughout my education: my mother for pretending to be interested in my research, and my father for continually making up medical acronyms. This thesis would not have been possible without coffee and dreams; for those I am thankful. And, of course, thank you to my faithful dog, Kobe, for his unconditional love and hilarious antics.

To all of the warriors who have overcome an eating disorder,
and those still on the brave path to recovery.

Chapter 1: Introduction

Eating disorders (ED) are prevalent psychiatric disorders that carry an increased risk of death, specifically in individuals diagnosed with Anorexia Nervosa (AN). Up to a third of deaths in AN may be sudden and attributed to cardiac causes, but risk factors and clinical practice in the face of cardiac mortality are not well defined. The work in this thesis aims to better define the cardiac electrophysiology changes observed in eating disorders and their risk of sudden death, or lack thereof. Specifically, we will describe costs associated with a similar multidisciplinary evaluation, perform a systematic review of current literature, analyze the electrocardiograms (ECGs) of individuals with AN during the acute phase and throughout clinical and pharmacological treatment, and present preliminary data of the use of a novel ECG recording.

1.1 Cardiac Electrophysiology and the Electrocardiogram

Each cardiac beat is the result of an electrical stimulation of each cardiac cell, leading to cellular contraction of muscle fibers. The impulse and following contractions are a result of ion movement across the cell membranes. The cardiac action potential describes the different phases of ion movement, from depolarization to repolarization of the membrane. The action potential corresponds to the cardiac cycle, in which the heart fills (diastole), contracts (systole), and relaxes back to baseline. Physicians and researchers are interested in cardiac electrophysiology as genetic or acquired changes in the cardiac cycle can predispose individuals to abnormal heart rhythms, or arrhythmias.

The electrocardiogram (ECG) is a widely accessible clinical tool used to systematically assess cardiac electrophysiology. Positive and negative electrodes record the electrical activity of the heart to produce a tracing in reference to time and voltage. In current practice, the 12-lead ECG is performed with 10 electrodes placed on the chest and limbs to obtain 12 vectors or viewpoints of the cardiac electric signal. The ECG is divided into different waves labelled alphabetically from P to T, each representing a different phase of the cardiac cycle. The P wave, QRS complex, QT segment and T-wave are notable divisions of the ECG. There

is a multitude of information to be gathered from 12-lead ECG recordings throughout all stages of disease from health, to diagnostics, to surveillance. Arrhythmias are captured and characterized by the ECG. Although cardiac risks in eating disorders have been described for decades, the ECG has not been systematically used across clinical practices throughout evaluation and treatment.

1.1.1   Heart Rate

The heart rate (HR), or pulse, describes the number of heartbeats per minute and is a useful diagnostic tool. Normal ranges for resting HR vary by age, sex, and athletic status, with 60 beats per minute (bpm) accepted as a general standard norm. On ECG, the HR can be manually measured, but is calculated by automated computer algorithms to acceptable clinical accuracy in most conditions through normal range. A slow HR (bradycardia, typically <50 bpm) or fast HR (tachycardia, typically >100 bpm) can pose a multitude of issues, from fatigue to exercise intolerance to syncope. Bradycardia is widely observed in acute AN, but generally normalizes with weight gain and treatment[2,3].

In the setting of AN, HR variability (HRV) is also of interest as a potential marker of cardiac comorbidity[4-6]. HRV is the variability in the time between each heart beat and an indirect marker of autonomic activity. Low HRV may independently represent an increased risk of sudden cardiac death.

1.1.2   Cardiac Repolarization & the QT Interval

The divisions of the ECG represent events in the cardiac cycle; in eating disorders and sudden death we are most interested in the QT interval, which represents cardiac repolarization. At the end of each cardiac action potential depolarization, the cardiomyocytes need to 'recover', or repolarize, to prepare for the next beat. During the repolarization phase, the ions that drive the cardiac cycle move in and out of the myocytes to reset electrochemical balances. While this is occurring, a new heartbeat cannot initiate. Cardiac repolarization is a clinically important predictor of arrhythmic risk, as a prolonged or shortened duration can precipitate potentially life-threatening arrhythmias[7]. As repolarization prolongs, abnormal

premature beats (early and late after depolarizations) may lead to arrhythmias or cardiac arrest.

The QT interval is an inverse function of HR and is generally measured on ECG from the onset of the QRS complex to the end of the T-wave, or its return to baseline voltage; this translates into the duration of ventricular repolarization (since depolarization is generally fixed). Accepted upper-limit norms vary by sex: QT intervals longer than 440msec in men or 460msec in women are defined as prolonged. A 20 msec borderline window is often applied above these cutoffs. Generally, a QT interval below 350ms is regarded as abnormally short.

Genetic conditions, drugs, and electrolyte imbalances can alter the QT interval; when shortened or lengthened outside normal range, the risk of arrhythmia is dramatically increased[7,8]. The activity of cardiac potassium and sodium channels govern QT interval duration, so this measurement is influenced by altered serum electrolytes. As such, the arrhythmic risk of altered serum electrolytes plays a large role in the clinical practice of routine bloodwork in ED, especially in the setting of binge/purge behavior and during refeeding.

1.1.2.1   QT Correction Formulae

As the QT interval is highly dependent on the heart rate, standardized formulae to correct and compare values are needed (corrected QT interval, QTc). These values are functionally corrected to a heart rate of 60 bpm, or 1 beat per second (1 Hz). Currently, the most widely used formula is Bazett's formula (QTc=QT/√RR, where the RR interval is measured in seconds on ECG preceding the QT interval); unfortunately, this correction formula is calibrated at 60 beats per minute and only adequate for a narrow HR range, with a linear relationship between a heart rate of 50 and 100 bpm in healthy controls [9,10]. This becomes highly relevant in patients with acute AN as pronounced bradycardia is more often present than not. The Framingham and Fridericia formulae are regarded as more accurate at a wider range of HR, and uptake in clinical settings is becoming more common, but not yet standard practice.

1.1.3   Sudden Cardiac Arrest and Death

The ECG has been extensively described in settings of sudden cardiac arrest (SCA) and sudden unexpected death (SUD), and is often used to help predict risk of a cardiac event[11,12]. Most notably, repolarization changes can increase the risk of ventricular arrhythmias. These arrhythmias, in turn, can lead to cardiac arrest or death. In some cases, precipitating symptoms, such as syncope or palpitations, can initiate investigation and the ECG may reveal risk factors for SCA and SUD. For example, in the congenital Long QT Syndrome (LQTS), a prolonged QT interval at rest or during exercise correlates to increased risk of SCA or SUD. As such, this risk can be managed through lifestyle modifications or medications. However, SCA may be the first sign of malady: in these cases, an ECG immediately preceding or following the arrest can be extremely clinically helpful in reaching a diagnosis and determining the cause of the event. The presence of prolonged QT in eating disorders is inconsistently reported, questioning the role of the ECG in assessing the risk of SCA and SUD in this population[2].

1.2   Eating Disorders

Eating disorders (ED) are psychiatric disorders with significant associated morbidity and mortality. Subclasses of ED include Anorexia Nervosa (AN), Bulimia Nervosa (BN), Binge-Eating Disorder (BED), and Other Specified/Unspecified Feeding and Eating Disorders (OSFED/UFED). AN is characterized by low weight and an intense fear of weight gain, and is the least common but most deadly ED [13,14]. BN and BED are defined by periods of binge-eating; the difference lies in counteracting purge behaviours in BN, such as the use of laxatives or self-induced emesis. OSFED/UFED, previously combined and referred to as Eating Disorders Not Otherwise Specified (EDNOS), is a "catchall" diagnosis to include clinically significant disordered eating which may not satisfy diagnostic criteria for another subclass. The major focus of this thesis is AN, with a minor focus on the catchall ED diagnoses (EDNOS and OSFED/UFED).

1.2.1   The Diagnostic and Statistical Manual of Mental Disorders

The Diagnostic and Statistical Manual of Mental Disorders (DSM) outlines the standardized guidelines used to categorize and diagnose ED[15,16]. The fifth and current edition (DSM-V), produced by the American Psychiatric Association, was published in 2013. Thus, researchers and clinicians are currently in a transition period between the previous fourth, text-revised (DSM-IV-TR; published in 2000) and DSM-V, as studies published and conceptualized with DSM-IV-TR criteria and definitions are still relevant.

Notable changes from DSM-IV-TR to DSM-V include the removal of amenorrhea as a diagnostic criterion for AN and redefinition of the 'catchall' categories. Amenorrhea was a controversial diagnostic criterion as it was irrelevant to premenarchal females and all males, and mainly served as a point of exclusion, as opposed to providing diagnostic value. In addition, the catchall diagnosis, previously referred to as EDNOS (Eating Disorder Not Otherwise Specified), was redefined to OSFED (Other Specified Feeding or Eating Disorder) and UFED (Undefined Feeding or Eating Disorder). Both OSFED and UFED capture clinically significant disordered eating behaviours, with OSFED generally representing individuals whose symptoms/behaviours do not quite satisfy AN or BN and UFED capturing the remaining cases. With the introduction of DSM-V, the relative prevalence of EDNOS decreased compared to OSFED/UFED. The bulk of this transition is due to the formalization of Binge Eating Disorder in DSM-V; however, a subset of patients were reassigned diagnoses as a result of the relaxation of AN and BN criteria.

As revisions to the DSM continue to be made, it is important for healthcare professionals to remain up to date on current diagnostic criteria. Although changing diagnoses may not be ideal for both clinicians and patients, this redefinition to move individuals out of the "catchall" categories can benefit treatment plans, forecast symptoms, and assist with patient identity[17].

1.2.2 Incidence and Prevalence of Eating Disorders

The true incidence and prevalence of ED are difficult to discern, as there are varying degrees of disease severity, studies present rates for different populations, and the age distribution of ED is heavily skewed towards adolescents. The majority of epidemiological data regarding ED incidence and prevalence hail from longitudinal European studies [18-21]. The reported incidence of ED in males and females combined by age 24 ranges from 0.34-0.62 per 100 individuals, with slight differences by diagnosis[18]. Since 1970, the population incidence of AN has remained relatively constant at 4.5-7.5 per 100,000 person-years [19,21,22]. However, smaller studies have presented lifetime incidences as high as 104 per 100,000 person-years[23]. Adolescent incidence is significantly increased compared to the general population, with rates up to 490 per 100,000 person-years for broad AN.

Over 40% of adolescents report disordered eating behaviors, while the combined female adolescent prevalence of any diagnosed ED is between 6-12% [22-25]. Similar to incidence, the lifetime prevalence of ED varies by diagnosis. In part due to the greater range of diagnoses, from broad to narrow AN, reported AN prevalence has a relatively large range from 1-4%[20,22,23,26]. With the redefinition of DSM-V criteria, diagnoses have been shunted into more specific eating disorder diagnoses, reducing the prevalence of catchall ED diagnoses. Forty-eight to 64 percent of all eating disorders were diagnosed as 'catchall' via DSM-IV-TR; via DSM-V this now accounts for 16-39% of diagnosed ED [25,27].

The vast majority of individuals affected by eating disorders are female. The lifetime prevalence of any ED in men is 0.3-0.7%, which is up to ten-fold lower than females[20,26,28]. Although reports of increasing male ED prevalence have surfaced, it is most likely that this rising prevalence is due to gained publicity and awareness and true epidemiology has followed the stability of female cases[29]. It is widely accepted that 20% of all ED cases are men. Further, adolescents are at highest risk of ED, with peak age of onset reported between 15-20 years of age[23]. This high-risk age group represents up to 40% of all cases of AN, with similar distributions in other ED[21].

1.2.3   Mortality

The mortality of the catchall diagnoses (EDNOS/OSFED/UFED) is difficult to discern and interpret, as symptoms and severity may differ greatly between patients. Nonetheless, the standardized mortality ratio (SMR) for EDNOS was estimated at 1.92, suggesting individuals are at an increased risk of death compared to the general population[30].

AN has the highest mortality of the eating disorders, and is the third leading cause of death in adolescent females[13,14,28]. Suicide accounts for 20-32% of deaths in this population; however, natural causes of death as a result of severe starvation also occur[30]. The SMR in all females with hospitalized AN was reported as 6.3 in a study of over 6000 females, and a meta-analysis of 36 studies reported an SMR of 5.86[13,30]. Reported SMR values reflect slightly different study populations as researchers do not always define identical sample/diagnostic parameters, making direct comparisons non-ideal. Nonetheless, a steady decline in annual risk was observed over 20 years of follow-up from first hospitalization, with a reduction in SMR from 19.3 to 3.5 at less than one to over twenty follow-up years[13]. One-third of reported AN-related deaths are attributed to cardiac causes (SMR 2.3), with many of these deaths occurring suddenly and unexpectedly (SUD)[13,31,32]. An autopsy study did not find conclusive structural evidence of pathology, suggesting the mechanism of death is ventricular arrhythmias stemming from abnormalities in cardiac electrophysiology that pose risk[32].

1.3   Anorexia Nervosa

DSM-V lists three diagnostic criteria for AN:

   A. Significantly low body weight (less than minimally normal or expected) due to a restriction of energy intake relative to requirements
   B. Intense fear of gaining weight or persistent behaviors to interfere with weight gain
   C. Distorted body image, influence of body weight or shape on self-evaluation, or consistent lack of acknowledgement of low body weight

Previous versions of the DSM specified Estimated Body Weight (EBW) or Body Mass Index (BMI; kg/m^2) values to satisfy the criterion of 'significantly low body weight'. However, a

standardized formula for calculating EBW was not specified and BMI is not a completely accurate assessment of body weight status, leading to non-standardized and possibly inaccurate diagnoses[33]. Similar to other ED, adolescent females are at the greatest risk of developing AN. Subpopulations, such as dancers, appear to be at higher risk of AN than other adolescent females[34]. Although the onset of AN typically occurs in adolescence or early adulthood, chronic AN can last a lifetime.

1.3.1   Sub-classifications of Anorexia Nervosa

The DSM-V Diagnostic Criteria apply to all individuals diagnosed with AN, but symptoms and behaviors can be further classified into Restrictive (AN-R), Binge-Eating/Purge (AN-BP) types. Generally, AN-R includes individuals whose low body weight is due to restriction of food intake and/or excessive exercise. Conversely, AN-BP includes individuals who have participated in binge-eating or purging behaviors in the past 3 months, including self-induced vomiting, or misuse of laxatives, or enemas. Behaviorally, AN-BP individuals may closely resemble those with BN, although the DSM-V diagnostic criteria differ.

A further sub-classification of AN is included in OSFED diagnoses by DSM-V: atypical AN. In atypical AN, individuals meet Criteria B and C, but maintain a normal or above normal body weight despite significant weight loss.

1.3.2   Anorexia Nervosa in Society

In Western society, thin bodies and low body weight are often celebrated; in the midst of an obesity epidemic, this may be beneficial in promoting healthful behaviors. However, this is not always the case. The societal glorification of low body weight can trigger psychological tendencies towards the development of AN[35]. In the fashion industry, models are expected to maintain dangerously low body weights and put disproportional value on physical appearance, potentially increasing environmental risk for AN; reform has begun in countries such as France and Italy, but resistance to lower weight limits has been dominant in North American modelling agencies[36,37]. Although ED and AN are generally regarded as "Western" conditions, the scope of these psychiatric disorders is worldwide. Pike et al. have outlined the

emergence of ED in Asia, and argue that although Western influence in the spike of ED prevalence is likely, culture-specific reactivity has also played a role in ED development and unique subtype tendencies [38,39].

1.3.3   The Risk Factors for Developing Anorexia Nervosa

The risk factors for developing Anorexia Nervosa are intertwined among nature and nurture; causative events are difficult to identify as a mix of genetic and environmental aspects often lead to the onset of AN.

The potential genetic component to developing AN has gained recent traction in the research realm. Machine learning studies are in their infancy, but provide immense potential in deciphering the complex polygenomics of AN and ED[40]. Nonetheless, the notion of familial AN is supported by studies examining relative risk and heritability, a measure of the genetic influence on certain phenotypes. For first-degree female relatives of females with AN, the relative risk is 11.3[41,42]. Given the female preponderance of AN, these values are difficult to calculate in men, but it is hypothesized that the risk of AN in first-degree male relatives of affected individuals is also elevated, albeit likely to a lesser degree. The heritability of AN is estimated at 0.56-0.74; however, it is important to note that heritability calculations are extremely sample-dependent and can varying greatly by geographic location and age[26,43]. Nonetheless, evidence of a genetic component of AN has been demonstrated and further research is expected.

One's immediate situational environment also appears to play a significant role in the onset of AN. Research into the etiology and risk factors for AN was redefined in the late 1990's by a series of studies that utilized the Oxford Risk Factor Interview, a methodological tool superior to those used in previous studies [44-47]. A 2008 study by Pike et al. identified correlated precipitating events to onset of AN [35]. Within the year prior to AN diagnosis, individuals were more likely to have experienced physical abuse or critical comments about shape, weight, or eating compared to individuals with no psychiatric diagnosis or a different psychiatric diagnosis, respectively. Perfectionism has been well linked to the development

and etiology of AN; it has recently been suggested that those with high perfectionism personality traits were specifically more likely to develop AN-R over AN-BP[35,44,48,49]. In contrast, a history of sexual abuse was more likely in those with AN-BP[35].

1.3.4   Disease Course and Treatment

The primary treatment goals in AN are weight gain and psychological recovery. Treatment plans are generally a combination of monitored food intake and individual and/or group cognitive behavioral therapy. Recovery durations vary greatly based on duration and severity of disease, patient characteristics, and other factors. Direct evaluation of weight restoration on disease parameters is complicated by the remission/relapse cycles observed in AN. The risk of relapse or non-recovery from acute AN is the highest of any ED, ranging from 30-48%[50-53]. Only half of patients were fully recovered at 21-year follow-up[52]. These statistics are clinically important as they suggest an upstream treatment is needed to reduce risk of relapse and ultimately cure AN. Cognitive behavioral therapy and other psychotherapy approaches targeting the psychiatric components of AN have been used, but the ideal treatment plan is likely multidisciplinary and patient-specific[54].

1.3.5   Comorbidities and Systemic Manifestations of AN

In comparison to the multisystem pathological manifestations observed in AN, the DSM-V diagnostic criteria are narrow. Notable additional manifestations of AN include serum electrolyte changes, mood disorders, cardiac abnormalities, substance abuse/addiction, Celiac disease, and diabetes; although these pathologies are not included in the diagnostic criteria, they still have a suspected link to AN behaviors and potential to complicate treatment and recovery[20]. The hemodynamic, psychiatric, and cardiac comorbidities are of most interest in the scope of this thesis work. Generally, these abnormalities normalize with weight gain[55-57].

1.3.5.1   Serum Electrolyte Imbalance

The most notable hemodynamic changes consistently observed in AN are reductions in serum electrolyte levels. Hypokalemia, hyponatremia, hypocalcemia, and hypomagnesemia are observed[58]. In AN, starvation is the most likely cause for these imbalances, but purging

behaviors such as emesis and laxative/diuretic misuse, may contribute. The degree of imbalance ranges greatly between patients and throughout treatment, making the prevalence of electrolyte imbalances difficult to quantify. Nonetheless, abnormalities are regarded as sufficiently common to encourage regular serum testing in acute AN and throughout refeeding to ensure restoration of electrolyte balance[59,60]. Abnormal electrolytes may play a role in subsequent comorbidities and manifestations of AN, notably with regards to cardiac electrophysiology.

In addition, serum electrolytes may become imbalanced during treatment for AN, notably in Refeeding Syndrome (RFS). As the body has worked to maintain a level of starvation homeostasis in AN, the shock of treatment refeeding protocols can create multisystem imbalances and may even be fatal. Most often, the electrolyte imbalances can be neutralized without major complication but require careful clinical observation to reduce risk of adverse events or death[61]. Among these, electrolyte abnormalities in RFS are likely linked with an increased risk of cardiac arrhythmias[58,62,63]. Notably, hypokalemia may occur; as both electrolytes are intricately involved in the cardiac action potential, this may pose an arrhythmic risk. With careful observation, it does not appear that the risk of RFS adverse events is heightened with a higher caloric diet than previously recommended[64].

1.3.5.2   Mood Disorders

Between 70-80% of individuals with AN are diagnosed with a concurrent mood disorder[20,65]. Depression and anxiety are the most commonly observed, suggesting a potential link in neuropathology, although this has yet to definitively described. The role of mood disorders in acute AN onset and disease course is unclear, as mood disorders have been reported to both precede and follow AN diagnosis[65]. Nonetheless, their presence in the majority of AN patients poses a common and complex conundrum for treatment plans.

The main point of conflict, and thus research interest, regarding mood disorders in AN is related to the psychopharmacotherapies prescribed. Commonly prescribed medication classes include Selective Serotonin Reuptake Inhibitors (SSRIs), and Atypical Antipsychotics

(AAPs) for the treatment of depressive and psychotic symptoms, respectively. Weight gain has been observed in normal weight individuals taking AAPs, and a combinatory benefit of prescribing this class of medication in AN was postulated[66-68]. However, the findings have not been conclusive and current NICE (2004) and WFSBP (2011) guidelines do not support the use of SSRI or AAP for the purpose of weight gain or psychiatric treatment in AN[69,70]. Regardless, 53-84% of AN patients are prescribed psychopharmacotherapy at some point during treatment, in direct contrast to the current guidelines and evidence-based research[71,72]. This poses an issue on many fronts, from cost effectiveness to patient safety. As described below and in the results of this thesis, SSRI and AAP may have potentially harmful effects in AN and ED, increasing the risk of morbidity and mortality.

1.3.5.3   Cardiac Abnormalities

Cardiac abnormalities in AN are observed in up to 80% of cases and contribute to one third of deaths[31]. Common findings can be separated into two categories: structural pathology and altered cardiac electrophysiology. Notably, SSRI and AAP may exacerbate cardiac electrophysiology changes. A systematic review of cardiac changes in AN was published in 2016, which outlines common cardiac abnormalities but also highlights the lack of evidence based causation for sudden death[3].

Structural pathologies include pericardial effusion and ventricular hypotrophy. Pericardial effusion, generally asymptomatic, is found in 22% of AN patients and normalizes with weight gain[73]. The etiology of these effusions is not well understood, but given the low symptom and complication rate, they are not generally regarded as clinically urgent. Secondly, decreased left ventricular mass is noted via echocardiography in as many as 93% of patients[74-76]. It is reasonable to speculate that the heart, as a muscle, reduces in mass, similar to the skeletal muscle mass in AN and starvation[77,78]. As the body returns to a more nourished state, the pericardial effusions resolve and the ventricular mass returns to normal [56].

Current literature surrounding the cardiac electrophysiologic changes observed in AN are further described in Section 1.4 – Heart Rhythms in Anorexia Nervosa. In brief, electrolyte imbalances may alter the electrocardiogram (ECG) in AN, although these changes may also be present in the absence of hemodynamic abnormalities[2,75]. The most common ECG abnormalities, and the focus of this thesis work, are bradycardia (low heart rate) and QT interval changes

1.4   Heart Rhythms in Anorexia Nervosa

In the context of the relatively high prevalence of ED and AN, heart rhythms and arrhythmias are understudied and poorly characterized. Bradycardia is consistently described in AN, while the degree of QT interval changes, or lack thereof, are not consistently reported.

1.4.1   Bradycardia

Bradycardia is widely described during acute AN. Guidelines do not specify a specific HR threshold at which to admit patients to the hospital, but a 2014 survey of physicians most commonly noted a lower threshold of 40 beats per minute[60]. Yahalom et al (2013) reported 70% of individuals with AN to have a resting HR below 50 beats per minute, while Padfield et al. (2016) did not find a difference in resting HR between adolescents with AN and healthy controls[75,79]. Regardless, a recent systematic review regarded bradycardia as the most consistent finding in AN, second to low weight[3]. Bradycardia is likely due to a multitude of factors, but heavily influenced by autonomic dysfunction and decreased basal metabolic rate as observed in starvation states[80,81].

1.4.2   QT Interval

A consensus on the resting QT interval in AN has not been reached; both a 2008 meta-analysis and 2016 systematic review reported non-conclusive evidence supporting shortened, normal, and lengthened QT intervals in individuals with AN compared to healthy controls[2,3]. Many studies are subject to the pitfall of inadequate QT correction formulae, as acute AN patients are bradycardic and Bazett's formula calculates shorter QTc than physiologic at slower HR: this is most apparent in studies where the absolute QT interval is longer, but the

QTc is shorter compared to healthy controls[82,83]. As previously mentioned, the QT interval is dependent on serum electrolytes levels, but abnormal QT dynamics have also been noted in the absence of such irregularities[56,75]. In the event that QT interval abnormalities are present during acute AN, normalization with weight gain is usually observed[84,85]. Interestingly though, there is conflicting data regarding a correlative link between QT interval length and BMI[83,86].

In congenital Long QT Syndrome (LQTS), abnormalities in the QT interval may require an increase in HR, such as during exercise, to be unmasked. As a result, individuals with LQTS are generally at higher risk of arrhythmia during periods of high HR. The arrhythmic mechanism of LQTS is widely described as Torsade de Pointes, however this or any specific form of ventricular arrhythmia has not been consistently described in AN[32,87]. Padfield et al. (2016) hypothesized a similar relationship between the QT interval and exercise in AN, and described maladaptive repolarization dynamics during exercise in AN compared to healthy controls, despite similar baseline QT intervals[75]. This finding has clinical significance as healthy reintroduction to exercise is a hallmark of AN treatment wherein patient risk must be scrutinized. Further, Padfield et al. described abnormalities at submaximal HR, suggesting risk of arrhythmia does not exclusively exist at high-intensity exercise in AN.

Similar to HR variability, irregularity in the QT interval can indicate an increased risk of arrhythmia; however, unlike HR variability, an increase in QT variability is pathologic. Also referred to as QT dispersion, this measurement is calculated as the difference between the leads with the longest and shortest QT intervals on a single 12-lead ECG. Day et al. (1990) described QT dispersion as a predictor of arrhythmia independent of QT interval in AN, and other studies have reported data in support of increased QT dispersion marking increased adverse risk[88,89].

1.5   Implications of Research

This thesis work aims to better define cardiac electrophysiology in eating disorders, holding potential to impact the cardiac evaluations of patients with ED, specifically AN. Cost and

economic data presented in Chapter 2 lay groundwork and highlights the necessity for an AN-specific cost analysis of cardiac testing, and potential cost-effectiveness calculations when considering both non-invasive and invasive testing and procedures. Chapter 3 presents results from one of the largest case-control ECG analyses of adolescents with AN and EDNOS, and is the first extensive dataset analyzing the QT interval and other ECG parameters in the presence of psychopharmacotherapy. A systematic review focused solely on the QT dynamics in AN has never been completed; the review included in Chapter 4 will be a useful tool for clinicians to reference when assessing the QT interval in AN patients. Finally, the preliminary data presented in Chapter 5 proposes the utility of novel ECG recording devices with potential to incorporate long-term monitoring in outpatient AN populations.

1.6   Overarching Hypotheses

This thesis aims to improve our understanding of heart rhythms in AN and EDNOS/OSFED/UFED, and lay the foundation for formal risk stratification. We postulate the following three overarching hypotheses:

1. Comprehensive cardiac testing is an effective and cost-efficient means of evaluation.
2. Psychopharmacotherapies will alter the ECG in the setting of AN and EDNOS/OSFED/UFED.
3. Cardiac repolarization in AN will differ from healthy controls and accepted norms at rest and during exercise.

Chapter 2: Cost Analysis of Patients Referred for Evaluation of Inherited Heart Rhythm Disorder

2.1 Summary

Background: Inherited heart rhythm disorders (IHRDs) are complex and uncommon arrhythmogenic conditions that can lead to sudden unexpected death in seemingly healthy individuals. Multidisciplinary programs can assist in the diagnostic testing of potentially affected individuals and their family members.

Methods: Patients evaluated in a specialized adult and pediatric IHRD clinic between April 2013 and February 2015 were characterized. The total costs per evaluation and diagnosis were calculated. Patients were divided according to referral indication (primary referral or family member).

Results: A total of 618 patients were evaluated (age 36±21 years; 52% male), of which 274 (44%) were primary referrals and 344 (56%) were family members referred for cascade screening. Overall, 47% had at least 1 follow-up visit. Patients had a median of 3 tests; primary referrals required more tests (4 vs 2; p<0.01). The median cost per patient was $1340 CAD. Evaluation of the primary referrals was costlier than family members ($3096 vs $983; p<0.01). A definite or probable diagnosis was determined in 464 patients (77%), with no difference according to patient type (p=0.18). The total cost per diagnosis was $4021 in primary referrals compared with $1277 in family members (p<0.01).

Conclusions: Clinical evaluation of patients with suspected IHRD results in a high diagnostic yield and costs aligned with other complex disorders involving multidisciplinary clinics. Evaluation costs are expectedly higher in primary referrals compared with targeted family screening.

2.2 Introduction

Inherited heart rhythm disorders (IHRDs) are uncommon and complex conditions that can

cause syncope, sudden cardiac arrest (SCA) and sudden unexpected death (SUD) in seemingly healthy individuals. A definitive IHRD diagnosis is often difficult because of test variability and the complexity of genetic underpinnings[90-95]. In addition to clinical testing, genetic sequencing can be helpful to identify a pathogenic variant and direct testing in potentially affected family members[95]. Unfortunately, a known pathogenic variant is found in less than half of IHRD families[92,96,97]. Arriving at the correct IHRD diagnosis is not straightforward, but is imperative to guide treatment, advise lifestyle changes, and assess risk.

The 4 most common IHRDs are long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and catecholaminergic polymorphic ventricular tachycardia. Each of these specific well described diagnoses have unique, but also overlapping clinical traits, which are further described in Appendix A.1[7,91,98,99].

Because of the complex clinical and genetic components of IHRD, a thorough evaluation is required and includes the specialized multidisciplinary expertise of adult and pediatric cardiac electrophysiologists, genetic counsellors, pathologists, laboratory clinicians, and nurses. As recommended by the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society guidelines, patients with diagnosed or suspected IHRD should be evaluated at a dedicated IHRD clinic; the British Columbia Inherited Arrhythmia Program (BCIAP) was established in 2013 on these guiding principles[91]. The Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER) has been led by multidisciplinary practices across Canada. In CASPER, patients with SCA/SUD and their first-degree family members were investigated, and it was shown that a systematic approach with phenotype-guided genetic testing can identify underlying IHRD[11,12,96,100,101].

Multidisciplinary IHRD clinics have improved awareness and management of primary cases of IHRD and the importance of cascade screening. As a result, more patients are evaluated for IHRD; this has led to an increased front-end cost for the health care system, balanced by

improved diagnosis and risk management[102-105]. Premature deaths might be prevented and result in a cost savings to society. The costs of comprehensive IHRD evaluation in a multidisciplinary clinic have not been formally reported or compared with other cardiac evaluations. We hypothesized that primary referrals would show more extensive and costly evaluations compared with family members, and that IHRD evaluation costs would compare favorably with other multidisciplinary clinics.

2.3   Methods

In 2013, the multidisciplinary BCIAP was founded in an effort to streamline assessment, diagnosis, and follow-up care of IHRD patients across sites in Vancouver and Victoria, British Columbia. Triage of referral information is directed by the genetic counsellor in consultation with the most responsible electrophysiologist. At the initial BCIAP visit, patients are seen by a genetic counsellor, electrophysiologist, and research staff. The team has access to a medical geneticist for consultation regarding genetic testing indications and interpretation (L.A., A.M.L.). The BCIAP team reviews the data, assesses which IHRD diagnosis might be present, if any, and arranges further clinical or genetic testing as indicated (Figure 2.1). As recommended by guidelines, follow-up and cascade screening of all first-degree family members is advocated[91,105].

2.3.1   Patients

Patients referred to the BCIAP in Vancouver, British Columbia, were included in this retrospective analysis of a prospectively enrolled observational cohort. Patients were classified as primary referrals or family members. Primary referrals were defined as those referred because of suspected IHRD without a previously known family history of IHRD or SCA/SUD. Family members were referred because of known or suspected family history of IHRD; the index case of each family (proband) was not always evaluated in the BCIAP. All data from patients evaluated between April 2013 and February 2015 were included. Criteria previously described by the CASPER investigators were used to categorize diagnoses as possible, probable, or definite (Table 2.1)[11]. The University of British Columbia research ethics board approved the study.

2.3.2   Evaluations

For the purpose of this study, 'test' refers to any phenotypic or genetic test, 'assessment' refers to an initial or follow-up clinic visit, and 'evaluation' refers to both tests and assessments combined. The composition of evaluations reflects the unique circumstances of each patient and the clinical course that the BCIAP deemed most effective and efficient, in keeping with current guidelines[94,95]. Each patient had at least 1 electrocardiogram (ECG) followed by a more diagnosis-specific series of testing. Panel sequencing (> 1 loci) was only offered to patients who stood to gain substantial diagnostic and treatment benefit and/or for the purpose of allowing cascade screening; panels included 13±9 genes[106]. Asymptomatic, investigation-negative patients only underwent single-locus genetic testing if an actionable (i.e. pathogenic) variant was identified in a first-degree family member.

2.3.3   Costs

The cost for each test was on the basis of the fee schedule of the 2015 British Columbia Medical Services Plan (MSP; Table 2.2). In cases in which tests were not directly billed to MSP, the cost was calculated by combining MSP billing codes to create an equivalent. Clinical assessment costs included clerical fees, genetic counsellor assessment, physician assessment, and associated costs. Costs of implantable cardioverter defibrillator (ICD) implantation and device follow-up were not included, because these were not directly incurred by the BCIAP. Genetic testing was divided into panel or single variant testing. The authors deemed $2300 CAD a representative value for panel testing, and $250 CAD for variant- specific testing ($1700 and $185 US and 1605 and 175 Euros, respectively, as of November 25, 2016). Because of the rapid evolution of specific genes tested within panels and associated costs, these estimates were applied to all patients where appropriate.

2.3.4   Data Analysis

The number of tests and total cost of evaluation were calculated for the total cohort and separated according to patient type. Genetic testing findings defined by the testing companies were used; a variant of unknown significance was not considered a positive result. Follow-up

assessment and discharge data were described. The cost per diagnosis was calculated, in which a diagnosis was defined as probable or definite[11] and cases in which IHRD was probably or definitely ruled out (unaffected). Diagnostic information before referral was described. In addition, the composition and cost of tests completed before referral to the BCIAP and after BCIAP referral were compared.

2.3.5 Statistical Methods

Categorical data were compared using χ^2 tests. The Shapiro-Wilk test was used to evaluate the data for normal distribution. Normally distributed continuous data were described as mean±SD and compared with a Student t-test. Non-normal continuous data were presented as median and interquartile range (IQR), and compared with a Mann-Whitney U test. All statistical analyses were performed using R Software, version 3.1.2 (The R Project for Statistical Computing, Vienna, Austria)[107].

2.4 Results

The cohort consisted of 618 patients (44% primary referrals, 52% male). The only significant demographic difference between patient types was age, with primary referrals significantly older (42 vs 31 years; Table 2.3). A total of 304 patients (49%) had at least 1 family member evaluated at the BCIAP. Every patient had an initial clinical assessment and standard ECG at the BCIAP (Figure 2.2). The most common tests were exercise stress test (58%) and echocardiogram (53%). Approximately half of the patients (47%) underwent genetic testing (53% panel, 47% single variant). The least common tests were cardiac computed tomography (4%) and electro- physiology study (2%). The mean number of each test per patient evaluated are shown in Table 2.1. Of patients who underwent Na^+ channel blocker challenge, 44% had previous unexplained SCA; in the remaining cases, this test was used to definitively rule in or out a Brugada syndrome phenotype. Patients had a median of 3 tests (excluding standard ECG; Figure 2.3), and primary referrals had significantly more tests than family members (4 vs 2; $p < 0.001$). The total median cost of evaluation per patient was $1340 (IQR, $789-$3165). Primary referrals incurred a significantly greater cost compared with family members ($3096 vs $983; $p < 0.011$; Figure 2.4).

The cost per diagnosis was calculated and is graphically represented in Figure 2.5. A probable or definite diagnosis was found in 474 patients (77%). This corresponded to a median cost of $1740 per diagnosis (IQR, $1025-$4111). When separated according to patient type, neither primary referrals (74%) nor family members (79%) were more likely to have an identified diagnosis (p = 0.18). There was a greater cost per diagnosis in primary referrals at $4021 (IQR, $1700-$5426), compared with $1277 in family members (IQR, $878-$2164; p < 0.01). A pathogenic variant was found in 50% of genetic testing, whereas a variant of unknown significance was found in 26% as reported by the testing company. There was no difference in patient type of those who underwent genetic testing (61% vs 54%; p = 0.08). The total cost per pathogenic variant identified in the subset of patients with genetic testing was $5376 (IQR, $1952-$7822).

During the study period, 292 patients had at least 1 follow-up assessment (47%), with a follow-up duration of 716±204 days and 2.0±1.6 in-clinic follow-up visits. There were 3 deaths (0.5%) and 140 (23%) patients were discharged from the BCIAP. Of the 3 deceased patients, 1 suffered from SUD and 2 died of unrelated causes. The individual who suffered SUD did not have a known premortem diagnosis after a standard cardiac testing applied to first-degree relatives of victims of SUD. Of 462 patients with available data, 3% of patients (n=6) experienced syncope during follow-up. An ICD was implanted in 123 cases (20%), with 22 (18%) for primary prevention and 101 (82%) for secondary prevention. Most ICDs were implanted in symptomatic primary referrals (n=108; 88%). Of the family members with ICDs (n = 9), 8 were implanted for primary prevention. Only 23 (19%) of ICDs were implanted after BCIAP evaluation; most were implanted after SCA as per recommended practice[108]. The most common diagnoses in patients with ICDs were long QT syndrome (21%), and arrhythmogenic right ventricular cardiomyopathy (17%). During the follow-up period, 18 patients (15%) had at least 1 ICD shock. One patient had an inappropriate shock due to T-wave oversensing. There was no difference between patient types discharged (p = 0.77). Most discharged patients were unaffected by IHRD or extremely low risk (73%), followed by patient-decided (Appendix A.2). Notably, in 15% of discharges the absence of a familial variant discovered by genetic testing resulted in discharge.

All tests were divided into pre- and post-referral to the BCIAP. The composition of tests varied according to time point (Appendix A.3). Tests more specific to IHRD were concentrated in the post-referral phase: 92% of signal- averaged ECG and 79% of drug infusions (epinephrine or Na^+ channel blocker) were completed after referral to BCIAP. The median number of evaluations as well as cost per patient were greater after referral to the BCIAP ($p < 0.001$; Appendices A.4 and A.5). Before evaluation at BCIAP, 92% of family members had < 5 tests completed (61% had none), suggesting that most family member evaluations were a result of BCIAP investigation.

Pre-referral data were available in 515 patients (249 primary referrals, Appendix A.6). Most patients were referred for evaluation by a family physician (n = 162; 31%), cardiologist (n = 108; 21%), or internally via BCIAP (n = 116; 23%). The diagnosis changed in 107 primary referrals. Notably, IHRD was ruled out in 21 primary referrals (7% of total primary referrals). There were 42 patients referred with a diagnosis of SCA; a probable or definite IHRD diagnosis was achieved in 13 (42%) and possible diagnosis in 15 (36%) patients.

Diagnosis data were available from 266 family members referred for cascade screening. Streamlined evaluation was completed in 146, because a known diagnosis was previously identified in the family. This diagnosis was confirmed in 52 patients (36%), and 72 (49%) were deemed unaffected. Of the 108 family members referred after a family history of SUD/SCA, a diagnosis of IHRD was found in 26 (24%) and 48 (44%) were deemed probably or definitely unaffected. The costs of evaluation were higher in family members referred after SUD/SCA ($1244 vs $1022; p = 0.008), although still lower than for primary referrals ($p < 0.001$).

2.5   Discussion

2.5.1   Rationale for Specialized Programs

Although published guidelines for the management of IHRD have advocated for specialized clinics since 2013, systematic evaluation of the utility and costs associated with such clinics is limited[91,102]. In a recent study with composition similar to this study, Adler et al.

investigated the clinical utility of a specialized IHRD program and reported a reduced incidence of cardiac events compared with patients without consistent specialized care[102].

A major benefit to specialized, multidisciplinary IHRD clinics is the ability to provide genetic counselling. IHRDs are genetically complex with the yield of panel testing between 9% and 64%[12,92,97]. In the largest analysis of genetic diagnosis, Hofman et al.[92] evaluated > 7000 patients at a specialized cardiogenetics clinic, identifying an uncertain likely pathogenic or pathogenic genetic variant in 31% of families, which is comparable with this study (37%). Genetic counselling services are imperative to ensure optimal psychological patient care, even when the pathogenicity of the variant is defined[109,110].

Although results presented in this study were from a single centre representing patients within a single province, the authors believe the findings are relatively generalizable to other similar international programs. Of course, the unique costs of each evaluation in other health systems will affect exact results, but we do not expect this to be drastic. A complication in the generalizability arises in that very few dedicated inherited arrhythmia programs exist worldwide, leaving many IHRD patients to be evaluated and followed in a less coordinated fashion; we expect this uncoordinated evaluation process leads to increased costs overall and advocate for specialized IHRD programs from a diagnostic as well as economic standpoint.

2.5.2   Cascade Screening

IHRD was probably or definitely ruled out in 56% of family members, reflecting the autosomal dominant nature of most IHRDs. This high proportion speaks to the importance of cascade screening and supports the formation of IHRD clinics to streamline this process; this can lead to better diagnoses of family members, guiding risk management and the need for therapies and follow-up.

2.5.3   Comparison with Other Complex Cardiac Diagnoses

The cost of evaluation for IHRD ($1340 CAD) falls within the range of other complex cardiac disorders involving multidisciplinary fields; studies have reported the cost per patient for evaluations of syncope, coronary artery disease, and outpatient atrial fibrillation to range

between $1000 and $9225 USD[111-114].

The cost per genetic diagnosis reported in this study ($5376 CAD) sits in the lower end of previously reported values ($5263-$21,441 USD)[97]. Genetic testing in a symptomatic subset of IHRD patients was found to be cost effective at $2500 USD per life year saved[115]; with continued follow-up and data collection, we hope to analyze cost effectiveness of IHRD genetic testing.

Regardless, most patients in this study were diagnosed with primarily phenotypic methods. Although genetic advances have improved IHRD diagnostic capability, phenotypic testing still holds substantial merit. A probable or definite diagnosis was reached in a greater proportion of this cohort compared with other IHRD studies[92,96]. Referrals to the BCIAP might be relatively streamlined, and patients are screened for suggestion of IHRD before testing. Although more data are needed to quantify the cost effectiveness of the implementation of a multidisciplinary IHRD clinic compared with general evaluation, the higher diagnostic rate suggests the BCIAP is an efficient use of resources to direct prevention strategies. Brief clinical outcome measures were described in this study because the focus was on the costs incurred; however, further investigation into the clinical outcomes of the BCIAP is warranted.

2.5.4   Variations According to Patient Type

Investigation of primary referrals was expectedly more extensive and costly compared with family members. Many primary referral evaluations begin with a 'clean slate,' whereas a specific IHRD diagnosis is suggested by the family history before family member evaluation. It is important to arrive at a positive or negative diagnosis in primary referrals to inform the need for cascade screening, thus a more extensive evaluation is often warranted[91]. A major contributor to the greater cost of primary referrals is panel genetic testing, although the cost of panel testing is decreasing.

Although primary referrals were significantly older (42±19 vs 30±21 years), we do not

expect that this affected results, because both cohorts were primarily adults. The age of IHRD onset ranges from 12 to 46 years, when evaluation of the proband and cascade screening is prompted[116-118]. Thus, cascade screening of children was likely, and the adult BCIAP contingency contributed most data to the evaluation.

2.5.5   Limitations

Because of the variation of IHRD presentation, the composition of evaluation varied greatly between patients. This variability is required to provide each patient with tailored testing and assessment regimens. We were unable to obtain data on the nature of care of the comparable period before the inception of the clinic. This is in part the reason for the creation of the BCIAP, but limits our ability to analyze the direct effect and calculate cost effectiveness. This is a single program study that involves care of 4.6 million people, limiting the generalizability of the data to other environments. Finally, indirect costs not included in MSP fee schedules could not be completely accounted for in the scope of this study; the true costs of evaluation are likely slightly higher but still within range of comparable complex cardiac diagnostic tests.

2.6   Conclusions

Clinical evaluation of patients with suspected inherited arrhythmia disorders results in a high diagnostic yield at costs aligned with other complex disorders involving multidisciplinary clinics. Evaluation costs are higher in primary referrals compared with targeted familial screening, with a comparable diagnostic rate. One can foresee that better case ascertainment and identification and streamlined care and follow-up after SCA/ SUD will lead to cost efficiencies in the future. The cost data presented may draw parallels to costs associated with an expanded cardiac evaluation in other conditions.

2.7   Relation to Eating Disorder Population

The ECG changes observed in some IHRD, specifically LQTS, have also been described in some patients with eating disorders; as a result, a trend towards more thorough cardiac evaluations in the eating disorder population has been observed[3]. This is in part because of

limited data suggesting an elevated risk of sudden cardiac death in patients with eating disorders, often associated with evidence of QT prolongation. Furthermore, there is evidence that 5-10% of patients with acquired Long QT, typically attributed to drug induced Long QT, in fact have a clear genetic predisposition to congenital Long QT[119,120]. Further, the costs of outpatient evaluation and treatment for eating disorders compare favorably to those reported in this study of IHRD, as a study of 566 individuals diagnosed with anorexia nervosa (AN) incurred outpatient costs of $2344±4735 US dollars[121]. IHRD and AN report similar standard mortality ratios (SMR) for SUD (1.5 and 2.3, respectively), and both require a multidisciplinary approach to achieve optimal care[13,122]. As such, both IHRD and eating disorders stand to contribute evidence to support the shift to multidisciplinary care while maintaining acceptable costs to, comparable to other related conditions.

2.8 Tables

Table 2.1 CASPER diagnostic strength criteria[11].

Level of diagnosis strength	Definition of diagnosis strength
Definite	Both clinical testing and genetic testing positive, or clinical testing clearly positive
Probable	Clinical testing or genetic testing positive (where genetic testing is available)
Possible	One or more clinical testing borderline but not conclusive

Table 2.2 Cost and number of investigations

Investigation	Cost (CAD $)	Total Patients Evaluated	Tests per Patient Evaluated
Clinical assessment – initial BCIAP visit	$360.19	618	1.00
Clinical assessment – follow-up	$125.26	292	1.99±1.62
Electrocardiogram (ECG)			
Standard ± High Lead	$33.10	618	3.95±4.24
Signal-Averaged ECG	$33.10	282	1.08±0.32
Holter Monitor	$142.31	229	1.42±1.26
Imaging			
Angiogram	$800.00	49	1.02±0.28
Cardiac CT	$450.00	26	1.00
Cardiac MRI	$641.00	127	1.10±0.35
Echocardiogram	$187.25	328	1.64±1.84
Right Ventricular Angiogram	$800.00	6	1.00
Provocation			
Electrophysiology Study	$761.24	13	1.00
Epinephrine Infusion	$542.12	44	1.00
Exercise Stress Test	$76.15	361	1.65±1.45
Procainamide Infusion	$601.13	66	1.02±0.12
Genetic Testing			
Comprehensive	$2300.00	194	1.00
Single Variant	$250.00	160	1.00

Table 2.3 Demographic characteristics

	Total Cohort	Primary Referrals	Family Members	P value
Male	299 (48%)	140 (47%)	159 (53%)	0.15
Age	36±21 years	42±19 years	31±21 years	<0.01
Known diagnosis (probable or definite) †	474 (77%)	203 (74%)	271 (79%)	0.14

†Probable diagnosis defined as clinical or genetic testing positive; definite diagnosis defined as clinical and genetic testing positive, or clinical testing clearly positive[96].

2.9 Figures
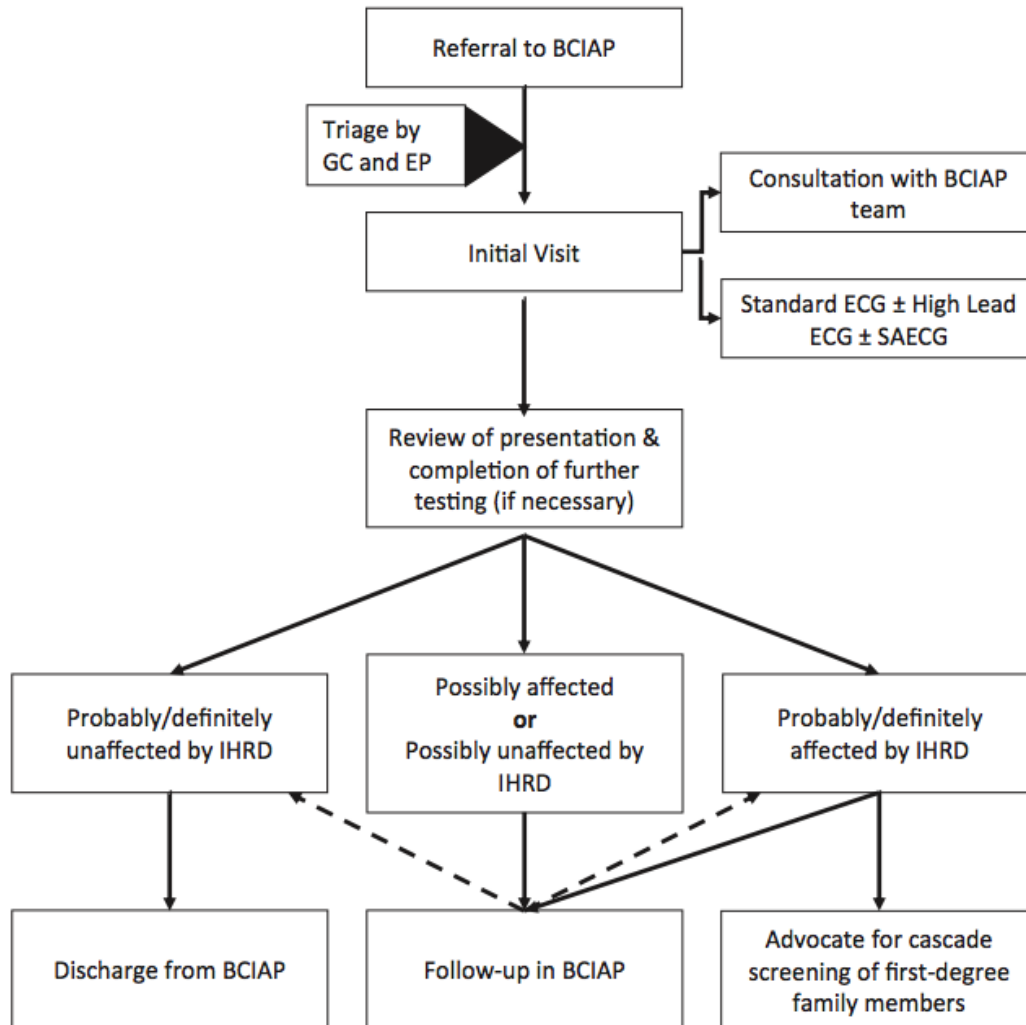
Figure 2.1 Inherited heart rhythm disorder (IHRD) evaluation flow chart.

A general flow chart of the British Columbia Inherited Arrhythmia Program (BCIAP) evaluation. ECG, electrocardiogram; EP, electrophysiologist; GC, genetic counsellor; SAECG, signal-averaged ECG.
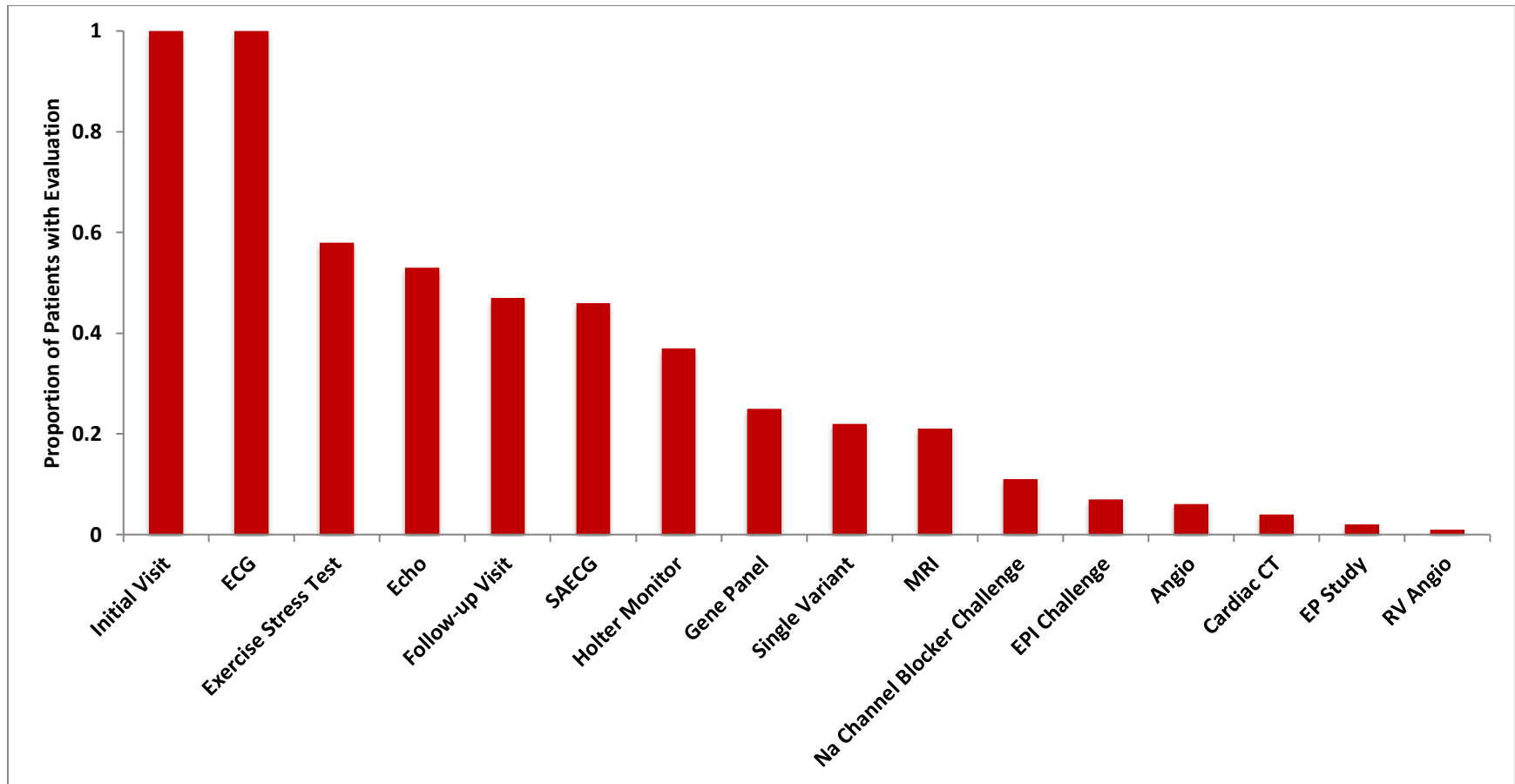
Figure 2.2 Distribution of evaluations.

The most common evaluations were initial clinical assessment by the BCIAP and standard ECG, followed by exercise stress test and echocardiogram. Very few patients had an Electrophysiology study, cardiac CT, or angiogram.
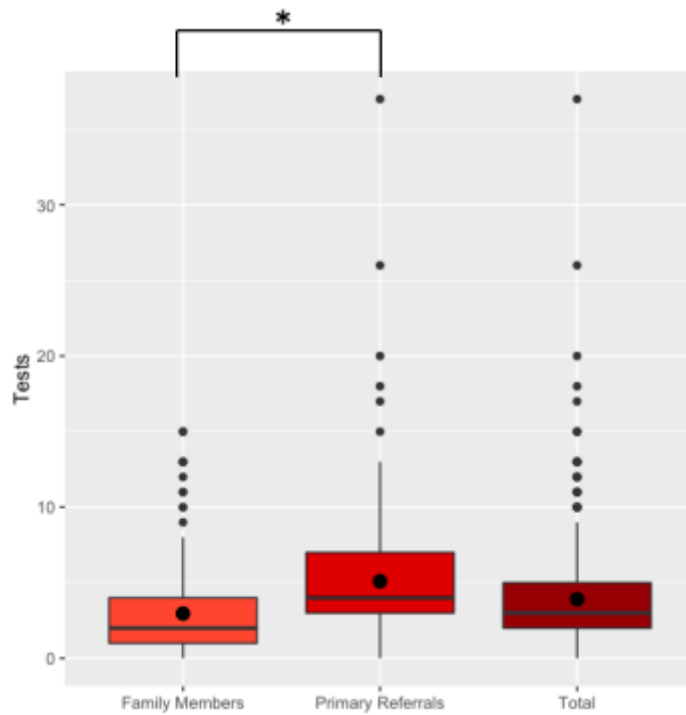
Figure 2.3 Number of tests

The total cohort had a median 3 tests excluding ECG (interquartile range [IQR] 2-5).   Primary referrals (4, IQR 3-7) had significantly more tests than family members (2, IQR 1-4; p < 0.001). Filled dot inside each box represents the mean. Two patients were excluded from this figure as they had > 20 tests as validated by the medical team, which included surveillance echocardiograms and Holter monitors.
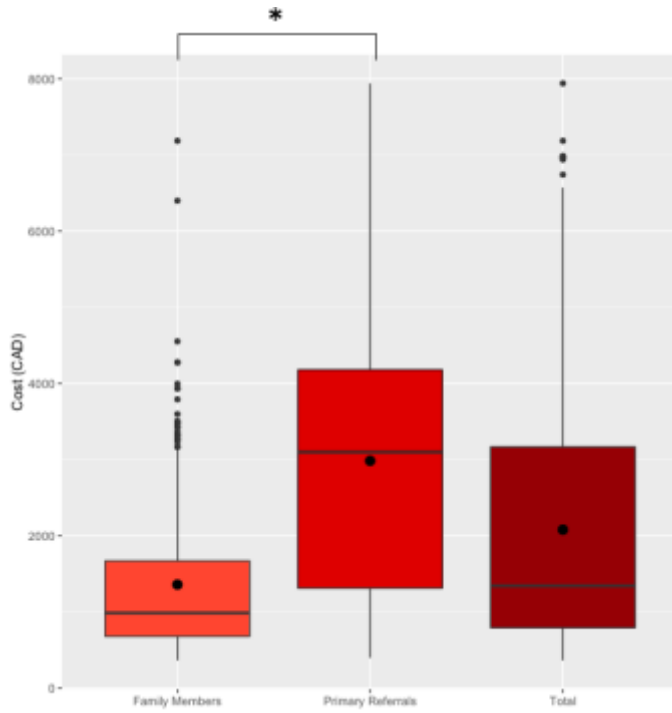
Figure 2.4 Cost per evaluation

The total cohort had a median cost of $1340 (IQR $789-3165). Evaluation of primary referrals ($3096, IQR $1309-4178) incurred significantly higher costs than family members ($983, IQR $676-1667, p < 0.001).
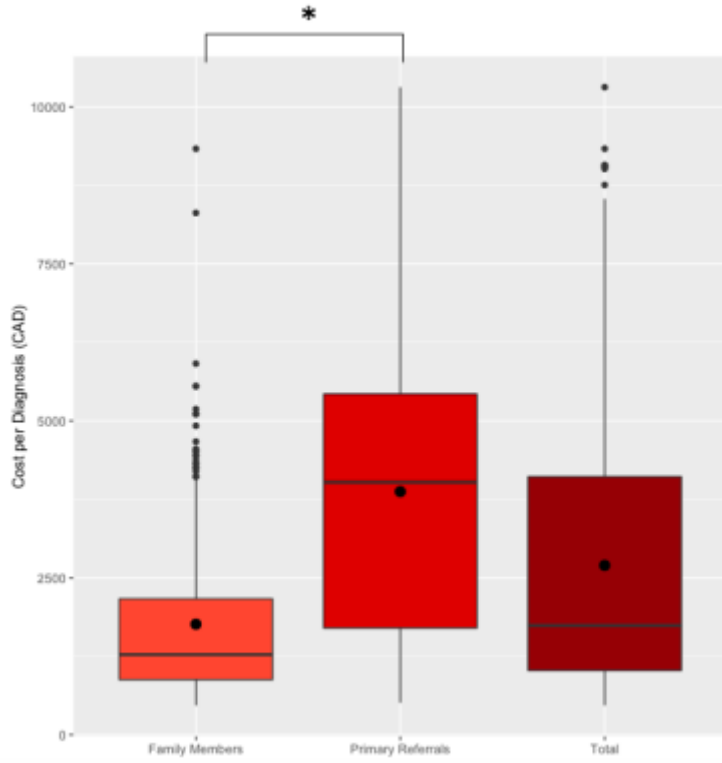
Figure 2.5 Cost per diagnosis

The median cost per diagnosis in the whole cohort was $1740 (IQR $1025-4111). The cost per diagnosis in primary referrals was significantly higher than that of family members ($4021 [$1700-5426] vs. $1277 [$878-2164], p < 0.001).

Chapter 3: Electrocardiographic Markers of Repolarization in Eating Disorders: A Case Control Study

3.1 Introduction

Eating disorders (ED) affect 1-2% of the population, with an increased prevalence in adolescent females[25]. Sudden unexpected death (SUD) is a leading cause of death in the eating disorder population, specifically those with anorexia nervosa (AN) and eating disorders not otherwise specified (EDNOS). Electrocardiographic changes have commonly been described, but are not yet well defined; specifically, changes in the QT interval may be present and contribute to SUD risk, but conflicting data hinders the ability to apply the findings clinically[2,3]. T-wave changes are commonly implicated in SUD risk in other conditions, but have only been described in three eating disorder case reports and never in a cohort[123-125]. Changes in the T-wave morphology, most notably inversion, have been associated with SUD risk in other populations[123]. The T-peak to T-end (Tpe) interval has been independently associated with SUD in cardiac disease and suggested as a marker of delayed repolarization that may increase the likelihood of ventricular arrhythmias[126]. Furthermore, 80% of eating disorder patients have concurrent mood disorders, often prompting prescription of psychopharmacotherapies which have well described QT prolonging effects in the normal weight population[65]. We sought to characterize ECG changes in AN and EDNOS and compare these to healthy controls.

3.2 Methods

A retrospective cohort study of adolescent females treated at the British Columbia Specialized Eating Disorders Clinic between 2010-2014 was performed. Age-matched healthy controls were recruited through flyers and retrospective ECGs were included from benign chest pain, syncope, or palpitation investigations; individuals with comorbid conditions and/or family history of Long QT Syndrome were excluded. Serum sodium and potassium levels were reported, with lower limits of normal set at 135 mmol/L and 3.5 mmol/L, respectively based on local laboratory standards. In circumstances where multiple ECG were performed, the ECG at the lowest BMI and therefore greatest disease severity was

used. Patients prescribed selective serotonin reuptake inhibitor (SSRI) and/or atypical anxiolytic (AAP) medications were included in the pharmacotherapy group. All resting ECGs were read with assessment of the HR, QT interval, and T-wave by trained reviewers blinded to case/control, pharmacological status and specific demographics. Bazett's formula was used to calculate corrected QT interval (QTc). T-wave dynamics were reported, including the interval from the peak of the T-wave to the end (Tpe) and T-wave morphology, which have both been shown to independently predict SUD in populations with cardiac disease[123,126]. Abnormal t-wave morphology was defined as notched, inverted, flattened, peaked, or U-waves as determined by the reviewers. Comparisons were made between patients and age-matched controls, and patients with or without medication.

3.3   Results

ECGs from 72 adolescents (65 females, age 15 ± 2 years, BMI 17.2 ± 2.8 kg/m^2) with a diagnosis of either AN (83%) or EDNOS (17%) were reviewed and compared to ECGs from 63 healthy age-matched controls. There were no differences in any reported parameters between female and male patients nor between AN and EDNOS (p=0.3-0.9). All patients had normal serum sodium levels, while one patient was mildly hypokalemic at closest measurement to ECG (3.2mmol/L, QTc 440ms). Nine patients had a current history of illicit drug use, most commonly marijuana (n=8) which has not been reported to prolong the QT interval.

3.3.1   Comparison to Healthy Controls

ED patients showed lower heart rates compared to controls (60 ± 17 vs. 72 ± 11 bpm, p<0.001), longer absolute QT intervals (405 ± 40 vs. 383 ± 24 ms, $p < 0.001$), and shorter QTc intervals (397 ± 34 vs. 423 ± 24 ms, p<0.001). At lowest BMI, two patients (3%) reported QTc intervals longer than the normal accepted range (>460ms), at 480 and 505ms in the absence of bradycardia (HR 60 and 79bpm, respectively). The shortest reported QTc interval was 379ms.

Abnormal T-waves were reported in 19 (26%) patient ECGs, with no difference in prevalence with regard to age, BMI, or medication status. The overall prevalence of any T-wave abnormality was not different between eating disorder patients and controls (26% vs. 14%, p=0.08), but the distribution of T-wave changes was different. Nine ED patients (14%) demonstrated T-wave flattening or inversion compared to 2 controls (3%; p=0.02). As shown in Figure 1, T-wave inversion was the most common abnormality in eating disorder patients, reported in 6 ECGs (8% overall) followed by the presence of U-waves. Seven controls with T-wave abnormalities had notched T-waves; one had T-wave inversion and one had flattening. Mean Tpe interval in eating disorder patients was 69±19m.vs 93±24ms in controls (p<0.001).

3.3.2 Effect of Psychopharmacotherapy on the ECG

Thirty ED patients (42%) received psychopharmacotherapy during treatment (1.5±0.6 medications per patient). There was no difference in BMI (p=0.14), QTc (p=0.14), or HR (p=0.13) of patients prescribed or not prescribed medications.

Concurrent ECGs were available both on and off medications in 13 unique patients, allowing for within group comparisons. There were no demographic differences within groups. When on medications, patients' heart rate and QTc increased minimally (3bpm and 7ms, p=0.50 and 0.47 respectively). While on medications, one patients' QTc lengthened to the upper limit of normal at 459ms from 440ms off medications.

3.4 Discussion

We have demonstrated that corrected QT intervals in eating disorder patients are in fact shorter in patients compared to controls, with all but two QTc within the normal range. In contradiction, a 2008 meta-analysis of ten studies reported overall significantly longer QTc intervals in AN patients compared to healthy controls[2]. A 2016 systematic review of cardiovascular complications in AN noted the heterogeneity of the current QT interval research reports, suggesting secondary causes such as hypokalemia and pharmacotherapy are more often contributors to altered QT dynamics than inherent to AN disease[3,86]. When

compared to healthy controls, QTc in ED have been described as shorter, similar, and longer, leaving much ambiguity in ECG interpretation[75,82,127-130]. Similar to other forms of acquired long QT, minor secondary factors likely influence the QT interval, with additional changes across varying severity and duration of disease. Although bradycardia is widely reported in AN, the study cohort did not have excessively low HR[3]. However, other parameters of disease severity (i.e. BMI) were similar across other studies, suggesting this cohort was likely still a reasonable representation of the population.

This is the first study to describe T-wave changes in an eating disorder cohort. The prevalence of changes in T-wave morphology were similar between patients and controls, but the clinical utility of this parameter lies in the type of abnormality. All but one T-wave abnormalities in healthy controls were classified as notched or inverted in lead V2, which have been described as a normal variant in adolescents[131,132]. None of the T-wave inversion observed in AN patients was in lead V2. T-wave inversion was reported in similar prevalence to the controls of study in athletic adolescents (1.5%), with lower prevalence in sedentary controls, and has been independently associated with SUD risk[123,133]. In addition, T-wave flattening has been described as an early marker of cardiac dysfunction[134]. This morphological change has only been described in case reports of hypokalemic anorexia nervosa patients[125,135]. The relatively high prevalence of T-wave inversion in this study (8%) suggests a potential contributor to the increased risk of SUD observed in eating disorder patients.

The decreased Tpe observed in patients compared to controls was unexpected. In fact, patient Tpe values were similar to those reported in over 300 controls in a separate study (76ms) while the controls of this study were more similar to the at-risk patient population (89ms)[136]. Interestingly, patients had longer QT intervals compared to controls, from which we would expect longer Tpe as opposed to the observed shorter duration[137]. At the cellular level, Tpe has been described as a measure of transmural repolarization; such a specific change in eating disorders is not impossible, although larger studies are needed to reach a more definitive conclusion[138].

Changes in the QT interval are dynamic over disease duration, severity, and other factors: it is likely that T-wave dynamics may show similar changes, and longitudinal ECG studies in eating disorders are warranted to better assess these changes and define risk[2].

Although not observed in this study, psychopharmacotherapy may increase the QT interval in eating disorder patients, although clinical relevance is uncertain. This supports the notion that certain individuals may be predisposed to QT prolongation, based on genetic and environmental factors such as SSRI and AAP administration, previously termed reduced repolarization reserve[75]. However, as supported by our data, the absolute risk incurred by psychopharmacotherapy is likely to be low. Nonetheless, use of these medications in the eating disorder population should be evaluated with caution as current guidelines do not support psychological or weight restoration benefits[69].

3.5   Conclusion

The ECG in eating disorder patients manifests several changes that include bradycardia and T-wave changes. QT changes support shorter corrected intervals compared to healthy controls. Psychopharmacotherapies do not appear to impact the ECG. Further studies investigating T-wave changes and clinical outcomes are necessary to discern the utility of this parameter, but given the previously well described association of T-wave changes with risk of SUD, this may be a promising risk marker that warrants systematic large-scale study.

3.6   Figure
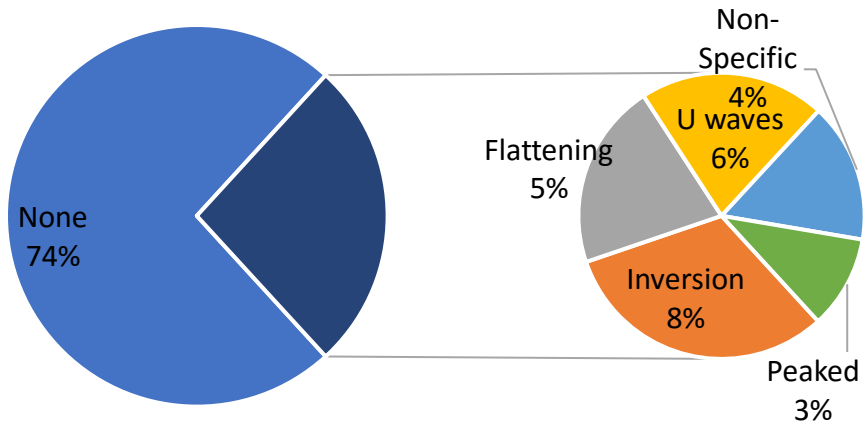
A. Eating disorder patients
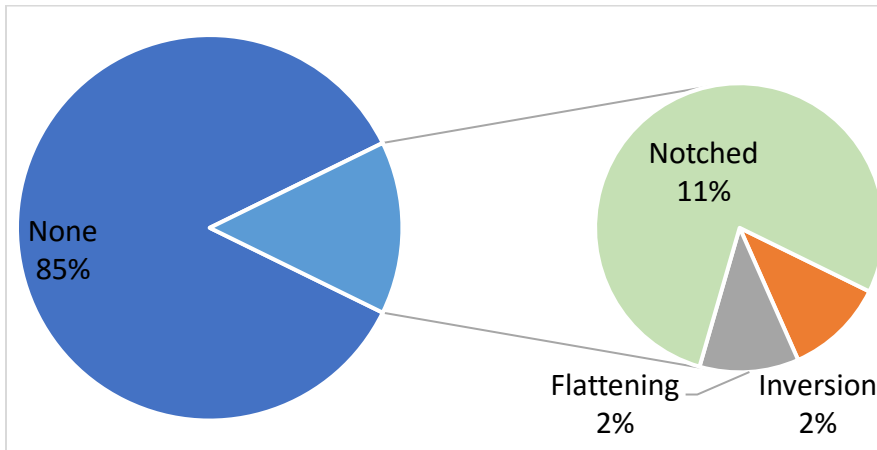
B. Healthy controls

Figure 3.1 Types of T-wave interval morphology changes in eating disorders.

There was no difference in the prevalence of any T-wave abnormality in ED patients compared to healthy controls (26% vs 14%, p=0.08). The combined prevalence of T-wave inversion or flattening was greater in ED patients (14% vs. 3%, p=0.02).

Chapter 4: The QT Interval in Anorexia Nervosa: a Systematic Review and Meta-Analysis

4.1 Summary

Individuals with anorexia nervosa (AN) have increased risk of mortality. Abnormal cardiac electrophysiology may play a role in this increased risk of sudden unexpected death (SUD); in other populations, the QT interval on electrocardiogram plays an important role in risk assessment wherein lifestyle changes and pharmacological therapies can limit this risk. A consensus surrounding alterations in the QT interval in AN, and subsequent therapies, has not been reached. We performed a systematic literature review and meta-analysis to examine the QT interval in AN, utilising Medline and EBMASE.

Twenty-six studies were included. Twenty-four studies reported mean or median corrected QT (QTc) interval values within clinically normal range for females (350-460ms). Meta-analyses did not suggest a difference in the QTc interval in AN compared to healthy controls, although AN patients did show greater variability in interlead QT measurements (QT dispersion; QTd).

Alteration in the QT interval, or lack thereof, in acute AN is not well enough defined to definitively inform clinical practice. Cardiac repolarization represents at best a minor risk factor for SUD in the AN population, with QTd a more likely useful assessment tool than resting QT interval. Clinicians should err on the side of caution and perform surveillance ECGs on individuals with AN to assess the QT interval, as this minimally invasive and relatively low cost test may provide useful insight.

4.2 Introduction

Anorexia nervosa (AN) affects 1% of the overall population with a concentrated prevalence in adolescent females [22,25]. AN has the highest mortality of any eating disorder, in part attributable to ventricular arrhythmia [32]. Alterations in cardiac repolarization have been

implicated, suggesting a role for the electrocardiogram (ECG) QT interval in risk-stratification. The QT interval is corrected for heart rate (QTc) since bradycardia is common in AN. A meta-analysis in 2008 of 10 AN studies revealed QTc intervals at the upper-limit of normal [2]. However, only 5 of the 10 studies reported electrolyte data, and potential QT-prolonging medications were not assessed. We recently described impaired repolarization reserve in AN during exercise, noting a significant number of more recent publication in this field [75]. We therefore performed a systematic review specific to the QT interval in AN to improve understanding of any changes present which may better inform clinical practice.

4.3   Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed (Appendix B.1). [139,140]

4.3.1   Search Strategy and Data Extraction

MEDLINE and EMBASE were searched from January 2000 to December 2016, limited to humans and English language, excluding case studies, reviews, and conference abstracts. Retrospective or prospective cohort, case-control, and cross-sectional studies were included. Search terms were determined by literature review, database query and consensus among authors. The search strategy is outlined in Appendix B.2. The search returned 226 unique records. Manual bibliography searches identified an additional 3 publications (Figure 4.1). Two reviewers (MJ and NM) screened titles and abstracts for inclusion with reconciliation through discussion. Collected variables were defined a priori, expanded after pilot review of initial studies, and collected in Microsoft Excel.

4.3.2   Population and Outcomes

The population was individuals diagnosed with AN. Studies with both AN and other eating disorders were included where AN data was presented separately. Outcomes of interest included the resting QTc interval, heart rate (HR), and QT dispersion (QTd). International guidelines define QT prolongation as abnormal and possibly indicative of long QT syndrome above 450ms and 460ms for males and females respectively[141-143]. However, the identified

studies were inconsistent and utilized borderline, definitely abnormal, and sex-specific thresholds. The following Medical Subject Headings (MeSH) and Emtree terms were used: anorexia nervosa; electrocardiogram and long QT syndrome. Additional keywords were employed including anorexia, eating disorder and QT. Extracted data included bibliographic details; sample size and population characteristics; anthropometric data; medication and electrolyte status; and QT interval and other ECG/cardiac parameters for AN subjects and healthy controls.

4.3.3 Study Quality and Analysis

Study quality was assessed as recommended by the Cochrane Collaboration and Institute of Medicine guidelines. Nine bias domains were selected (sampling, inclusion/exclusion, protocol deviation, follow-up, validity, harm reporting, measurement, confounders, and detection) based on the Cochrane Collaboration Risk of Bias Tool and Handbook and Agency for Healthcare Research and Quality RTI Item Banks[144-146]. Each domain was assigned as high, low, or unclear risk of bias for each study.

4.3.4 Data Synthesis

Weighted averages of mean QTc and QTd in patients with AN and controls were calculated using the DerSimonian-Laird random effects model.[147] Differences between AN and controls were assessed using weighted mean differences and Hedges' g statistic. Forest plots of estimates with 95% confidence intervals (CI) were generated. Publication bias was assessed through visual inspection of funnel plots and the Begg-Mazumdar rank correlation test for asymmetry.[148,149] Heterogeneity was tested with visual forest plot inspection, Cochrane Q (p<0.01) and I^2 statistics.[150] This demonstrated significant heterogeneity which is explored (I^2 > 90%).

4.4   Results

4.4.1   Population

Twenty-six studies comprising 1193 individuals with AN were identified (Table 4.1). Most studies (22/26) were small (<50 participants), 3 included between 50-100 participants, and only one study exceeded 100 participants (n=330). Twenty-two studies addressed AN alone, the remaining 4 reporting AN alongside other eating disorders. Seventeen studies included control data. Study participants' mean age ranged from 14 to 29 years with most between 14 to 16 years. Echocardiography was performed in 10 studies which all reported normal left ventricular (LV) ejection fraction. LV mass was significantly lower compared to controls in all 8 studies which reported values (Table 4.2).

4.4.2   Study Quality

The risk of bias was low in most domains (Figure 4.2, Appendix B.3 and B.4). Most studies were small, prospective cohorts. A trained reviewer manually measured the QT interval in 62% of studies; the reviewer was also blinded in 69% of those studies read manually. However, twelve studies had a high risk of bias as established repolarization mediators such as electrolyte and medication status were not assessed.

4.4.3   QTc Interval at Baseline/Single Time-Point

Sixteen studies including 964 patients compared QTc in AN versus age- and sex-matched controls (Table 4.2). Respectively, mean QTc was 405ms (95% CI 398–412ms) compared to 398ms (95% CI 389–408ms) (Figure 4.3, Panels A and B). No significant difference was found in the weighted mean difference between patients with AN and controls (Hedges' g statistic -0.21 (95% CI -0.78 to 0.36), p=0.43).

Sixteen studies reported the proportion of participants with prolonged QTc using different cutoffs (440-500ms). Six reported no patients and 10 studies reported 1-40% of patients with prolonged QTc. The single large study of 330 AN participants observed a mean QTc of 388ms with QT prolongation in 4.2% of participants, defined as QTc >440ms [151].

4.4.4   Factors Affecting QTc Calculation

Twenty-four studies reported HR (Table 4.2). AN patients had significantly slower HR compared to controls in 12 of 16 studies. Resting bradycardia, defined as <60 bpm, was reported in 15 studies. Two studies (n=38, all female and n=23, 20 female) reported mean values <50 bpm. The method of QT correction was reported in 20 studies, most utilizing Bazett's formula (n=17), with one study using each of Framingham, Fridericia, and Hodges (Table 4.2). The latter compared common QT correction formulae across 100 female AN inpatients and concluded Hodges was optimal as it showed the smallest correlation to HR [152].

4.4.5   QTc Interval at Follow-Up

Only 7 studies reported QTc at baseline and follow-up, 5 reporting no change and 2 significant shortening (Table 4.3). The latter studies are confounded by both potassium supplementation and refeeding responses (notably resolution of bradycardia). In the first study (n=28), absolute QT lengthened and QTc shortened after 4 weeks with compared to without potassium supplementation[153]. The second study reported significant QT shortening relative to baseline after one year of refeeding in 11 females [154].

4.4.6   QT Prolonging Factors

Potential QT prolonging factors were rarely reported with the exception of electrolytes and prescribed drugs. No study reported illicit drugs, while LQTS and diabetes mellitus were reported in 2 and 3 studies respectively (Appendix B.6). Medication status was available in 12 studies: 6 included patients receiving psychopharmacotherapy, 4 reported no patients on medications, 1 excluded and 1 stopped medications before ECG recording. Serum electrolytes were reported in 16 studies. All reported mean serum potassium levels within normal range. Eight studies reported no hypokalemic individuals, while 5 studies reported hypokalemia in 3-32% of patients (Table 4.1). Four studies reported correlation of serum electrolytes with only one finding a significant correlation with QTc (Appendix B.5) [124]. No consistent relationship was observed between QTc and BMI.

4.4.7 QT Dispersion (QTd)

Eight studies including 499 patients compared QTd in AN versus age- and sex-matched controls. Respectively, mean QTd was significantly increased in AN 53ms (95% CI 42–64ms) compared to controls 34ms (95% CI 29–39ms) (Figure 4.4, Panels A and B). The weighted mean difference was significantly increased in patients with AN relative to controls (Hedges' g statistic -1.37 (95% CI -2.46 to -0.28), p<0.01).

4.4.8 Sudden Death

One sudden unexpected death (SUD) was reported across all studies i.e. 1/1194 (0.08%) [155].

4.5 Discussion

This study demonstrates the following key findings in patients with AN: 1) mean QTc was not significantly increased; 2) mean QTd was increased; 3) resting bradycardia was common; 4) QT was mainly corrected using Bazett's formula, despite the recognized under-correction associated with bradycardia [152,156]; 5) non-standardized and often low thresholds for a female population e.g. 440ms were used to define abnormal; 6) confounding factors associated with both AN and QT prolongation were rarely systematically examined or reported; and 7) the incidence of sudden death was low.

4.5.1 The QTc Interval in Anorexia Nervosa

Our results contradict a meta-analysis of 10 studies in 2008 which reported longer QTc intervals in AN patients compared to healthy controls[2]. However, that analysis calculated mean values using simple weightings. Our analysis includes 3 times as many patients (964 vs. 316), more recent data, and utilizes random effects methods to pool QTc intervals for comparison to controls.

4.5.2   QTd in Anorexia Nervosa

QT dispersion (QTd), the ECG inter-lead variation of the QT interval, represents repolarization heterogeneity [88,89,157]. QTd is associated with high anxiety and psychopharmacotherapy use [158-160]. Increased QTd is most often concurrently reported with prolonged QTc. However, isolated QTd has been described in the absence of prolonged QTc[161]. As such, increased QTd in the AN population may represent a marker for SUD risk and warrants further investigation. In addition, it has been suggested that increased QTd may be linked to T-wave morphology, potentially introducing a new ECG parameter into the conversation[162].

4.5.3   Bradycardia and the QT Correction Formulae

Bradycardia (HR < 60bpm) is the commonest cardiac manifestation of AN and often used to guide clinical care although no evidence-based guidelines exist [3,163,164]. QT correction formulae have varying accuracy in the setting of bradycardia, with Bazett's formula often deemed inferior although it remains the most widely used[9,10,152]. The replacement of Bazett's formula is hindered by the lack of a definitive superior alternative. Nonetheless, QT correction discrepancies further complicate the heterogeneous upper cutoffs utilized, ranging from 440-500ms. Long QT syndrome guidelines suggest borderline upper limits of normal as 450ms in men and 460ms in women, with definitive abnormal values above 480ms[87,141]. However, the variable study-specific cutoffs restrict the ability to effectively compare or conduct standardized statistical analyses of the proportion of patients with QT prolongation.

4.5.4   Risks for Bias

The lack of standardized reporting of established causes of QT prolongation also associated with AN (i.e. known repolarization mediators) was surprising. Serum electrolytes are important in regulating the QT interval and cardiac repolarization, but QT changes were reported in the presence and absence of abnormal electrolyte levels. Studies either failed to report of excluded patients prescribed psychopharmacotherapies. The latter significantly impairs the generalizability of findings, since 53-84% of patients with AN are prescribed at

least one medication [71,72]. No studies commented on illicit drug use, although drug use is not uncommon in the AN population[165]. A combination of serum electrolytes, medications, and other consequences of AN and treatment may be responsible for changes in the QT interval. Varying proportions of AN patients' QTc intervals were deemed prolonged (1-40%), although inconsistent cutoffs were used. This suggests that although risk may be low, a subset of vulnerable patients may exist although case-control studies with consistent methodologies are needed to definitively define risk.

4.5.5   Sudden Unexpected Death in AN

Measuring repolarization (QT, QTc, QTd) is intuitively attractive as a tool for assessing sudden death risk. However, the lack of significant difference in QTc between AN and controls, high inter-study heterogeneity, and inability to adjust for unmeasured confounders and mediators, all suggest far more research is needed to understand any potential application. As importantly, sudden death events are rare, making direct causal inferences exceptionally challenging [166]. A study of 6009 females with AN observed 11 cardiac deaths and reported a Standardized Mortality Ratio of 2.3[13]. Our review identified only 1 death in 1194 patients (0.8%). Nonetheless, the QT interval and QTd are relatively simple, cheap and actionable measurements. However, standardized measurement, correction, thresholds, frequency of screening, and treatments all remain to be determined.

4.5.6   Directions for Future Research

More detailed and standardized datasets and reporting are needed to understand repolarization, QT changes and arrhythmic SUD risk in AN. Important variables to consider are medication status and the presence of potential cardiac modifiers (e.g. smoking, diabetes, history of syncope). Consistency across patient populations, testing parameters, and analyses will be important to better compare research. Additionally, the QT interval is highly dependent on HR and only one study in this review analyzed the QT interval over increasing HR[75]. This is the first meta-analysis to review QTd, which may present a more useful parameter to monitor SUD risk compared to resting QTc interval. Large-scale longitudinal studies are needed to directly assess cardiac repolarization changes and mortality risk in AN.

46

4.5.7 Limitations

Most studies were small, single centre cohorts. Insufficient information was presented for meta-regression or adjustment for repolarization mediators, notably medication and electrolyte status. Full text of 10 studies were not accessible or available in English.

4.6 Conclusion

The current research investigating the QTc interval in anorexia nervosa is heterogeneous both in design and results. At present, a direct link between cardiac repolarization and SUD has not be definitively identified in AN, although it does not appear likely that the QTc interval plays a large role. However, QTd may be a more active marker in the small but concerning risk of SUD. Regardless, the data supports that cardiac repolarization is an indicator of potential SUD risk in at best a subset of vulnerable patients. Further, large scale representative studies are required to determine whether or not ECG changes can predict arrhythmic risk and mortality in AN.

4.7 Tables

Table 4.1 – Study demographics and patient characteristics.

Study	n	Female (%)	Age Mean ± SD/SE* or mean (IQR)	BMI Mean ± SD/SE*	Duration of Illness Months; mean ± SD/SE* or median (IQR)	Patients on Medications (n)	Patient Location	Patients with Hypokalemia (%)	LVEF Mean ± SD or median (IQR) (%)	LV Mass Mean ± SD (g)	Controls (n)
Biadi[128]	19	100%	23.1 ± 5.2	14.0 ± 1.4	106 ± 86	0; stopped 24-48 hours pre-test	Mixed	0%	NR	NR	20
Billeci[82]	27	100%	14.6 ± 2.2	15.7 ± 2.1	18 ± 14	NR	Inpatient	0%	64 (60-72)	NR	15
DiVasta[167]	38	100%	16.2 ± 2.2	15.9 ± 1.8	NR	NR	Inpatient	3%	66 ± 5	100.1 ± 23.8	-
Ertugrul[129]	40	79%	14.9 ± 1.6	15.8 ± 2.7	NR	NR	Mixed	-	NR	NR	47
Facchini[86]	29	100%	22 ± 5	13.8 ± 1.5	NR	0	Inpatient	10%	69 ± 8	NR	14
Franzoni[153]	28	100%	20.1 ± 4.5	15.9 ± 2.4	NR	0	Outpatient	NR	NR	NR	20
Galetta[89]	16	100%	21.3 ± 4	15.7 ±1.9	27 ± 20	0	Outpatient	32%	66 ± 6	82.9 ± 17.1	16
Galetta[4]	25	100%	17.5 ± 4.2	15.3 ± 1.4	31 ± 22	0	NR	0%	65 ± 6	82.7 ± 15.3	25
Krantz[155]	6	100%	29 ± 3.2	16.2 ± 0.4	19 ± 11	NR	Outpatient	NR	NR	NR	10
Krantz[168]	19	95%	25.1 ± 5.5*	12.3 ±1.8*	NR	13	Inpatient	21%	67 ± 7	70.9 ± 20.8	-
Mont[56]	31	81%	15.7 ± 1.4	15.2 ± 2.0	NR	5 (first eval), 14 (second eval)	Mixed	0%	66 ± 6	84 ± 20	-
Nahshoni[169]	30	100%	15.7 ± 8.8	15.2 ± 1.6	26 ± 20	22 (after treatment)	Inpatient	0%	NR	NR	-
Nussinovitch[170]	43	93%	22.1 ± 3.4	18.0 ± 2.4	NR	25	Mixed	0%	NR	NR	45
O'Connor[64]	36	94%	13.8 ± 1.8	13.5 ± 1.1	NR	NR	Inpatient	0%	NR	NR	-
Olivares[171]	40	100%	15.5 (12.1-18.5)	15.3 ± 2.1	NR	NR	Inpatient	-	NR	76.8 ± 17.7	40
Padfield[75]	61	100%	15.6 ± 1.9	16.7 ± 2.0	14 (7-24)	38	Mixed	0%	67 ± 5	NR	45
Panagiotopoulos[127]	62	95%	15.1 ± 1.4	16 ± 2	10 (median; IQR NR)	NR	Outpatient	NR	NR	NR	97
Peebles[151]	330	100%	15.3	NR	14	NR	Mixed	NR	NR	NR	-
Roche[172]	25	92%	NR	15.2 ± 2.1	NR	NR	NR	-	NR	NR	25
Roche[85]	10	100%	19 ± 3	14.7 ± 2.3	NR	NR	NR	-	NR	NR	10
Takimoto[173]	47	100%	21.6 ± 6.0	15.2 ± 1.7	NR	Excluded	NR	Excluded	NR	NR	-
Ulger[154]	11	100%	15.0 ± 1.2	13.7 ± 1.5	NR	NR	Inpatient	-	80 ± 8	53.0 ± 14.3	12
Vanderdonckt[124]	47	96%	22.0 ± 8.2	14.7 ± 2.7	NR	13	NR	27%	NR	NR	-
Vazquez[174]	30	100%	15.5 ± 1.6	15.3 ± 2.1	NR	NR	Outpatient	-	65 ± 5	76.2 ± 22.6	30

48

Study	n	Female (%)	Age Mean ± SD/SE* or mean (IQR)	BMI Mean ± SD/SE*	Duration of Illness Months; mean ± SD/SE* or median (IQR)	Patients on Medications (n)	Patient Location	Patients with Hypokalemia (%)	LVEF Mean ± SD or median (IQR) (%)	LV Mass Mean ± SD (g)	Controls (n)
Walter[152]	100	100%	NR	10-17 (range)	NR	NR	Inpatient	-	NR	NR	-
Yahalom[79]	23	87%	15.7 ± 2.2	15.6 ± 2.4	NR	NR	NR	-	NR	NR	10

NR: not reported; SD: standard deviation; SE: standard error

Table 4.2 Cardiac parameters.

Study	HR Mean ± SD/SE* or median (IQR) (bpm)	QT Mean ± SD (ms)	QT Correction Formula Used	QTc Mean ± SD/SE* or median (IQR) (ms)	Controls Mean QTc ± SD/SE* P value vs AN	Threshold of Prolonged QTc	Prolonged QT N, %	HR Variability Mean ± SD or median (IQR) (LF/HF)	Control HR Variability Mean ± SD; P value vs. AN	QT/QTc* Dispersion Mean ± SD/SE^ (ms)	Control QT/QTc* Variability Mean ± SD/SE^; P value vs. AN
Biadi[128]	80 ± 18	NR	Bazett	380 ± 20	370 ± 30; 0.32	NR	0	NR	NR	NR	NR
Billeci[82]	65 ± 11	393 ± 23	Bazett	405 ± 25	428 ± 7.5; 0.001	440	0	0.7 (0.4-1.3)	2.1 (0.9-5.3); 0.002	NR	NR
DiVasta[167]	49 ± 16	450 ± 50	NR	400 ± 30	-	NR	NR	NR	NR	40 ± 20	-
Ertugrul[129]	65 ± 14	NR	NR	413 ± 29	414 ± 17.5; 0.81	440	6, 13%	NR	NR	NR	NR
Facchini[86]	55 ± 11	406 ± 35	Bazett	392 ± 25	407 ± 17; 0.08	480	0	1.8 ± 1.4	3.7 ± 2.6; 0.006	27 ± 12	23 ± 10; 0.21
Franzoni[153]	50 ± 11	457 ± 23	Bazett	407 ± 23	376 ± 20; <0.001	NR	NR	NR	NR	62 ± 12	31 ± 6; <0.001
Galetta[89]	53 ± 15	458 ± 33	Bazett	NR	-	NR	NR	NR	NR	50 ± 14	35 ± 6; 0.001
Galetta[4]	51 ± 12	NR	NR	404 ± 18	402 ± 22; NS	NR	NR	4.2 ± 1.3	6.8 ± 1.3; <0.001	NR	NR
Krantz[155]	61 ± 3*	NR	Bazett	415 ± 12*	409 ± 6*; 0.6	NR	NR	NR	NR	67 ± 6^	26 ± 3^; 0.001
Krantz[168]	53 (45-70)	452 ± 78	Fridericia	415 (403-445)	-	450	4, 21%	NR	NR	NR	NR
Mont[56]	53 ± 17	411 ± 41	NR	391 ± 18	-	440	0	NR	NR	42 ± 13	-
Nahshoni[169]	NR	471 ± 52	Bazett	464 ± 37	-	NR	NR	NR	NR	70 ± 16	-
Nussinovitch[170]	63	380 ± 26	Bazett	394 ± 30	390 ± 18; NS	NR	NR	NR	NR	NR	NR
O'Connor[64]	52 ± 7	431 ± 33	Framingham	405 ± 27	-	NR	5, 15%	NR	NR	NR	NR
Olivares[171]	57 ± 12	NR	Bazett	433 ± 34	401 ± 17; <0.05	440	3, 8%	NR	NR	53 ± 23	36 ± 24; <0.05
Padfield[75]	74 ± 15	NR	Bazett	416 ± 29	426 ± 24; 0.06	460	6, 10%	NR	NR	NR	NR
Panagiotopoulos[127]	58 ± 16	NR	Bazett	392 ± 26	406 ± 20; 0.002	NR	NR	NR	NR	41 ± 25*	50 ± 21*; 0.02
Peebles[151]	56 ± NR	NR	NR	388	-	NR	NR	NR	NR	NR	NR
Roche[172]	65 ± 11	377 ± 29	Bazett	399 ± 18	417 ± 12; <0.01	440	1, 10%	1.3 ± 0.7	2.0 ± 1.0; <0.02	NR	NR
Roche[85]	73 ± 12	374 ± 29	Bazett	388 ± 20	412 ± 14; <0.05	440	0	1.4 ± 1.4	2.0 ± 1.0; NS	NR	NR
Takimoto[173]	NR	NR	Bazett	470 ± 27	-	NR	NR	NR	NR	55 ± 16	-
Ulger[154]	61 ± 8	415 ± 40.34	Bazett	424 ± 29	376 ± 25; <0.0001	440	3, 27%	NR	Inpatient	71 ± 30	30 ± 13; <0.0001

Study	HR Mean ± SD/SE* or median (IQR) (bpm)	QT Mean ± SD (ms)	QT Correction Formula Used	QTc Mean ± SD/SE* or median (IQR) (ms)	Controls Mean QTc ± SD/SE* P value vs AN	Threshold of Prolonged QTc	Prolonged QT N, %	HR Variability Mean ± SD or median (IQR) (LF/HF)	Control HR Variability Mean ± SD; P value vs. AN	QT/QTc* Dispersion Mean ± SD/SE^ (ms)	Control QT/QTc* Variability Mean ± SD/SE^; P value vs. AN
Vanderdonckt[124]	81% of patients <60 bpm	413 ± 44	Bazett	382 ± 30	-	450	1, 2%	NR	NR	NR	NR
Vazquez[174]	57 ± 12	439 ± 36	Bazett	436 ± 36	391 ± 24; 0.001	440	12, 40%	NR	Outpatient	59 ± 23	38 ± 8; 0.000
Walter[152]	57 ± 12	417 ± 40	Hodge's	412 ± 31	-	500	1, 1%	NR	Inpatient	NR	NR
Yahalom[79]	44 ± 12	NR	NR	390 ± 24	340 ± 18; <0.001	NR	0	NR	NR	NR	NR

HF/LF: high/low frequency; HR: heart rate (bpm); LV: left ventricle; LVEF: left ventricular ejection fraction; NR: not reported; NS: not significant

Table 4.3 Follow-up data and changes in the QTc interval.

Study	Follow-up duration (measurement)	Follow-up QTc AN Mean ± SD (ms)	Follow-up QTc Control	P value: AN vs. Control	P value: AN Baseline vs. Follow-up
DiVasta[167]	121 days (median)	390 ± 20	-	-	NS
Franzoni[153]	28 days (value)	389 ± 21	407 ± 3	<0.05	<0.05
Mont[56]	7.9 ± 3.7 months (mean ± SD)	399 ± 22	-	-	0.081
Nahshoni[169]	"weight restored"	469 ± 32	-	-	0.505
Olivares[130]	9-18 months (range)	409 ± 26	403 ± 15	NR	0.000
Roche[85]	5 ± 2 months (median ± SD)	410 ± 28	412 ± 14	NS	NS
Ulger[154]	1 year refeeding (value)	390 ± 37	376 ± 25	NS	<0.0001

AN: anorexia nervosa; NR: not reported; NS: not significant

4.8   Figures
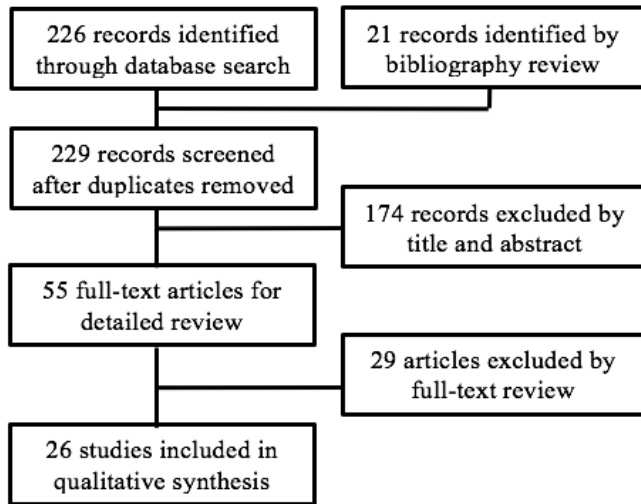
Figure 4.1 PRISMA flow diagram of study selection.

Studies were identified through database search (MEDLINE/EMBASE) and bibliography review.
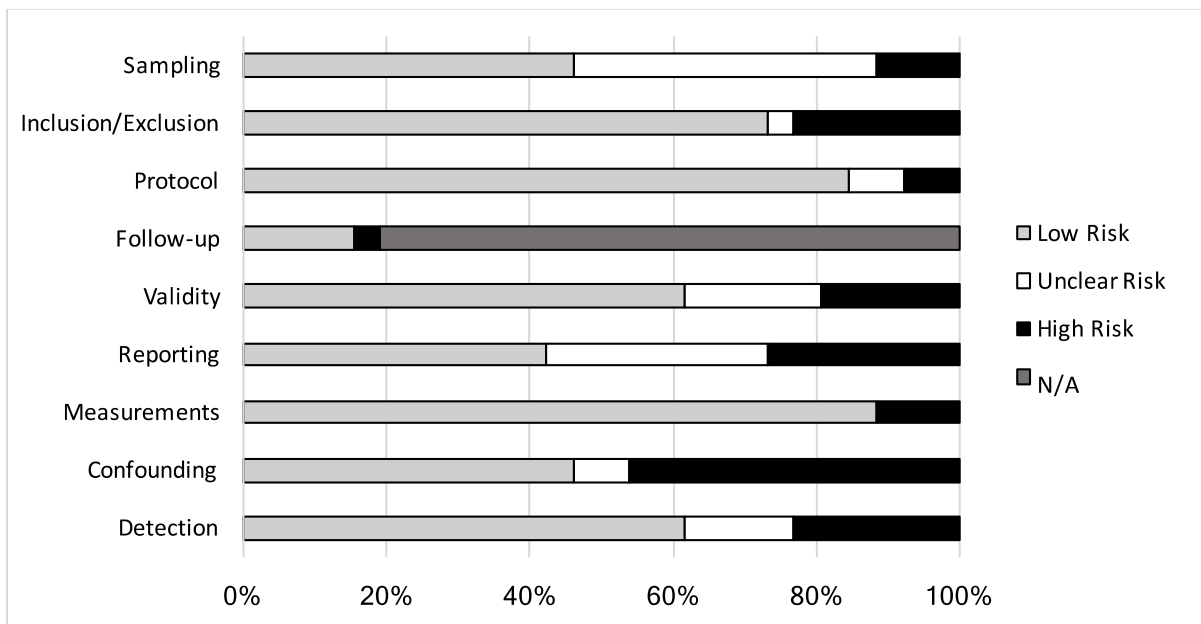
Figure 4.2 – Risk of bias summary.

Study bias was assessed on nine parameters adapted from the Cochrane Collaboration Risk of Bias Tool and Handbook and Agency for Healthcare Research and Quality RTI Item Banks. The majority of parameters revealed low risk of bias. Adjustment for confounding variables ("Confounding") was most commonly produced a high risk of bias, while deviations from protocol ("Protocol") and loss of patients to follow-up ("Follow-Up") did not often contribute high risk.

53

A. Mean QTc in patients with anorexia nervosa	B. Mean QTc in age- sex- matched controls
Pooled QTc 405 ms (95% CI 398 – 412ms)	Pooled QTc 398 ms (95% CI 389 – 408ms)
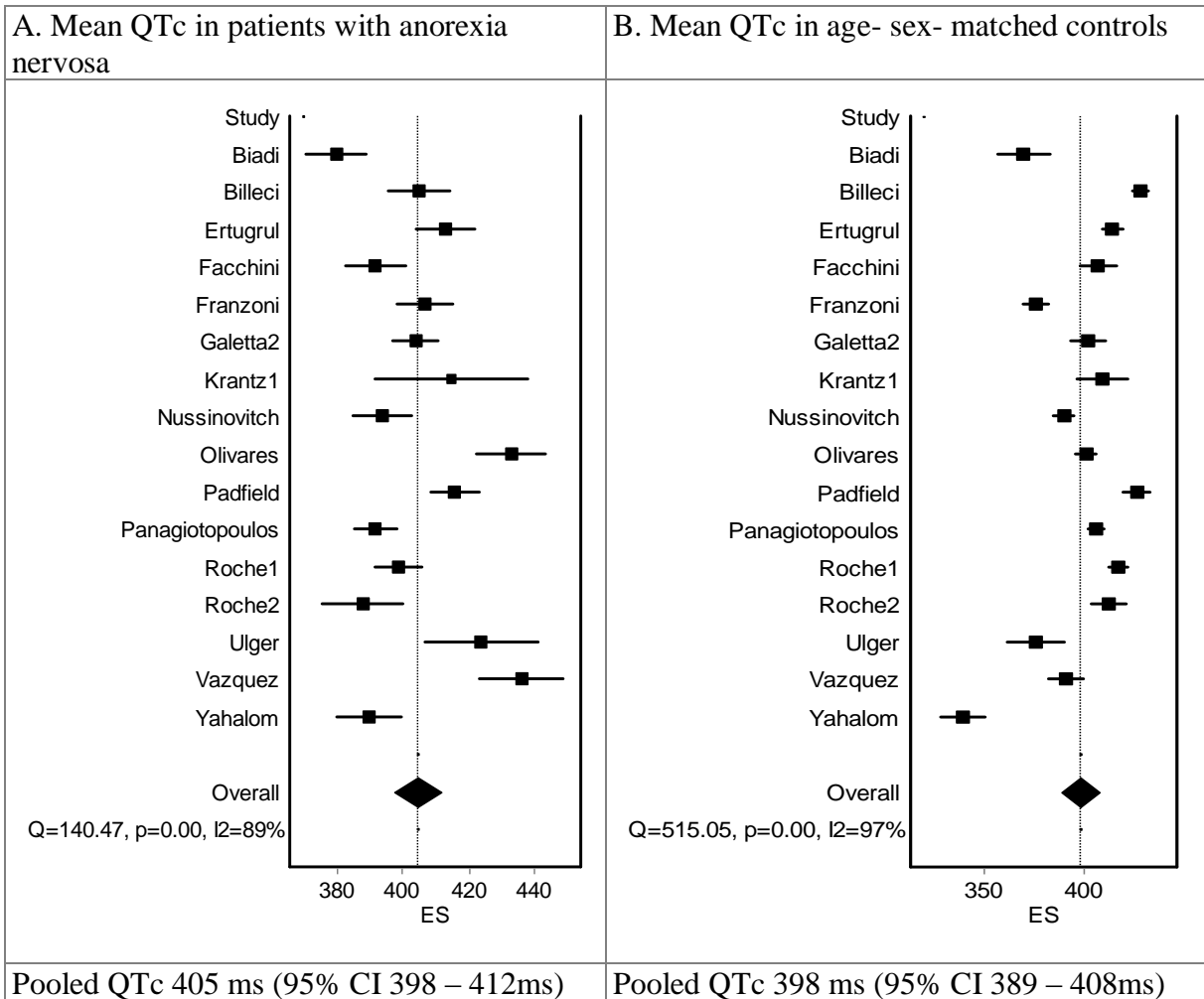
Figure 4.3 – Mean corrected QT interval (QTc) in patients with anorexia nervosa compared to controls.

Sixteen studies compared mean QTc of anorexia nervosa (AN) patients to controls. Pooled QTc mean in 964 AN patients was 405ms (95% CI 398-412ms) compared to pooled QTc in controls of 398ms (95% CI 389-408ms). There was no difference between the two groups (Hedge's g-statistic -0.21 (95% CI -0.78-0.30); p=0.43).

A. Mean QT dispersion in patients with anorexia	B. Mean QT dispersion in age- sex- matched controls

Pooled QT dispersion 53ms (95% CI 42–64ms)

Pooled QT dispersion 34ms (95% CI 29–39ms)
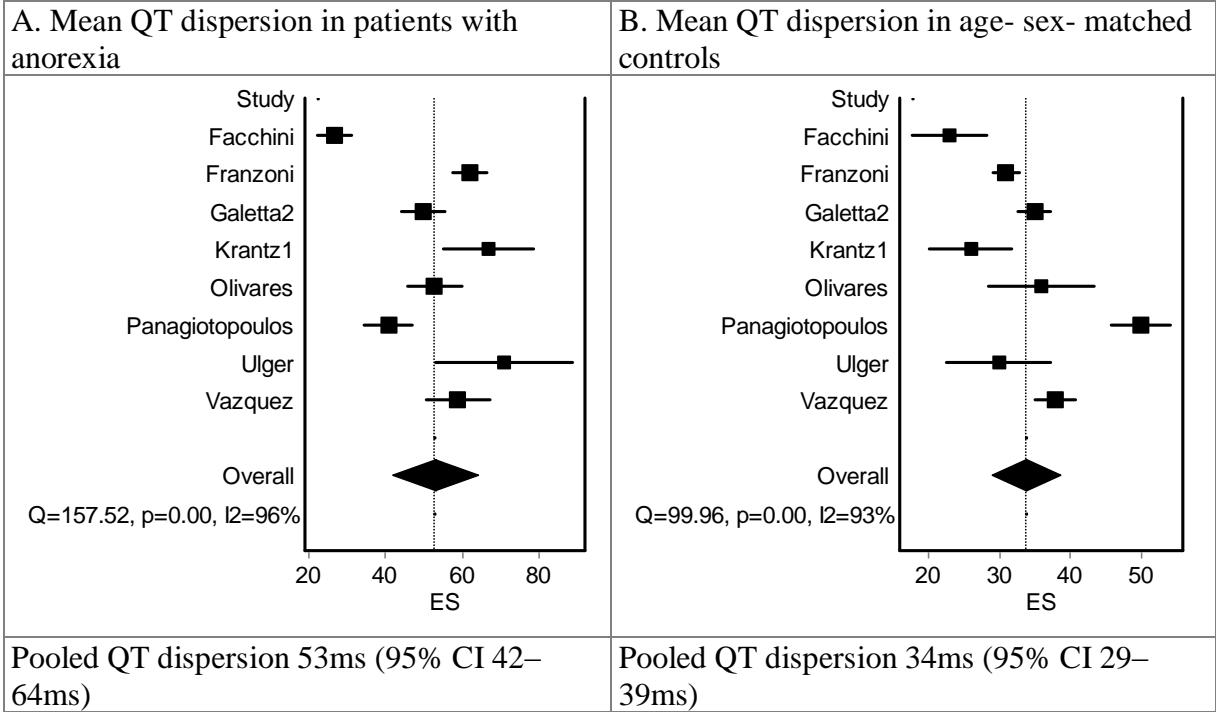
Figure 4.4 – Mean QT dispersion (QTd) in patietns with anorexia nervosa compared to controls

Eight studies compared mean QTd of anorexia nervosa (AN) patients to controls. Pooled QTc mean in 499 AN patients was 53ms (95% CI 42-64ms) compared to pooled QTd in controls of 34ms (95% CI 29-39ms). Greater QTd was observed in AN patients (Hedge's g-statistic -1.37 (95% CI -2.46 to -0.28); p<0.01).

Chapter 5: Evaluation of the Exercise Electrocardiogram in Anorexia Nervosa

5.1   Summary

Background

Anorexia Nervosa (AN) is an eating disorder characterized by low body weight, distorted body image, and an intense fear of gaining weight. Electrocardiogram (ECG) changes, particularly in the QT interval, have been implicated in AN but not well defined. Due to the increased risk of sudden death in AN, investigating QT adaptation to autonomic changes during exercise and recovery is important in understanding risk and guiding potential treatment.

Methods/Results

Previous retrospective data suggested that the resting QT interval is normal, but QT adaptation to exercise is abnormal. We explored this in a prospective observational cohort design using structured exercise monitoring. Patients were prospectively enrolled from the St. Paul's Hospital Provincial Adult Tertiary Eating Disorders Program and underwent a 6-minute modified stress test protocol: 1 minute supine, 1 minute standing, 2 minutes walking at regular pace, and 1 minute supine. The Icentia CardioSTAT device was used to record a Lead I equivalent ECG throughout the protocol; data was analyzed for HR and QT intervals. Preliminary data is reported in 11 AN patients (10 female) that provided informed consent and completed testing (age 31 ± 13 years, BMI 16.21 ± 1.3 kg/m^2). The corrected QT interval (QTc) was significantly longer at maximum HR compared to baseline and recovery ($p<0.01$). Matched control data was available for 4 AN patients, who did not show prolonged QTc at maximum HR ($p=0.13$). There were no differences between AN patients and controls at similar stages of exercise. Further, at similar heart rates, there was no difference in QTc between AN patients and healthy controls ($p=0.49$).

Conclusion

Low intensity exercise testing with a patch based recording device is feasible in deconditioned AN patients. At rest, individuals with AN appear to have normal QTc intervals. However, during exercise, the QTc prolongs and potentially represents increased

risk. Future data will include 3-month follow-up testing and expanded healthy control enrolment, in addition to more comprehensive ECG analyses.

5.2   Introduction

Eating disorders (ED) are complex psychiatric disorders associated with severe physical and psychological symptoms. While the greatest prevalence and incidence occur during adolescence, 25-29% of patients relapse throughout adulthood which may be triggered by stressful life events[23,175,176]. In addition, adult-onset ED comprises up to 10% of cases, although subclinical symptoms usually begin during adolescence[18]. ED are further classified by the Diagnostic and Statistical Manual (DSM-V) into anorexia nervosa, bulimia nervosa, binge eating disorder, and other feeding and eating disorders[177].

Anorexia nervosa (AN) is the least common ED but carries the highest mortality. Many of these deaths are sudden and may be in part due to cardiac arrhythmia[32]. As such, the electrocardiogram (ECG) is a useful tool to assess sudden unexpected death (SUD) risk as changes, specifically involving cardiac repolarization, have been implicated in SUD in AN and other conditions[32,88,96,133,178]. Repolarization changes in the QT interval have been studied in acute AN, but a consensus on the changes, and thus risk, has not been reached; studies report findings of shortened, unchanged, and prolonged QT intervals compared to healthy contols[2,3,82,129,154]. Further, the T-peak to end interval (Tpe), measured from the peak of the T-wave to return to the isoelectric line, has also been described as an arrhythmic risk factor but has not been studied in the AN population[126].

It is well documented that QT interval changes pose the most SUD risk during adrenergic states[93]. To date, only one study has analyzed the QT interval during exercise in AN patients, which identified impaired repolarization reserve at submaximal heart rates[75]. Two contributors to the lack of exercise-based AN research are the contraindication of exercise in acute AN and cumbersome nature of standard ECG recording devices. Exercise is often contraindicated on the basis of symptom interruption (over-exercising is a common behavioural manifestation of AN), as previous concerns of patient safety are not supported by

evidence[179]. The data reported by Padfield et al. (2016) suggests impaired repolarization can be quantified in the AN population without extensive exercise, supporting the notion that QT dynamics can effectively be assessed at low-level, controlled exercise while encouraging symptom interruption. Secondly, standard 12-lead ECG recording methods are cumbersome and require patients to undress which can be stressful given the low self-esteem and impaired body image characteristic of AN. An alternative, less invasive recording device may ease patient anxiety without compromising data collection.

We aimed to prospectively assess the QT interval with a modified exercise protocol targeting patients with anorexia nervosa using a novel minimally invasive device.

5.3   Methods

5.3.1   Patients

Patients were prospectively recruited from the British Columbia Provincial Adult Tertiary Eating Disorder Program from January to May 2017. All inpatients were invited to participate in the study and those who provided informed consent were enrolled. To facilitate inpatient comradery and limit exclusiveness, all ED diagnoses were approached to participate, although those diagnosed with AN were the primary target population. Non-AN patients with diagnosed ED were not included in this preliminary analysis. Where possible, height and weight measured on the same day as testing were used; otherwise, measurements taken within one week were used. Given the psychological impact of weigh-ins, only measurements taken for clinical purposes were used. Personal cardiac symptoms (syncope, chest pain, palpitations, cardiac arrest) and family history of SUD or LQTS were recorded. Prescribed medications were noted with special attention to cardiac medications (beta-blocker, ACE inhibitor, etc.) or those with known cardiac effects (antidepressants, anxiolytics, etc.). The most recent available serum potassium levels were reported, with hypokalemia defined as <3.5mmol/L based on local laboratory standards. Current diagnosis and previous treatment history were recorded. Duration of illness was measured from the reported time of symptom onset. Purging behaviour (laxative or emetic) is well documented to alter the ECG characteristics[180,181]. The most recent date of purge behaviour was recorded,

but no patients engaged in purging behaviour once admitted to hospital. The study was approved by the University of British Columbia Research Ethics Board.

5.3.2   Healthy Controls

Age- and sex-matched controls were recruited through flyers and in person by the research staff. Controls were directly matched for age and sex to eating disorder patients and provided informed consent. Controls taking any cardiac, SSRI, or AAP medications, with a personal history of a cardiac condition, or a family history of Long QT Syndrome were excluded.

5.3.3   ECG Protocol

The iCentia CardioSTAT device was used to record a modified lead I ECG in patients; this device is approved by Health Canada and the British Standards Institution for cardiac monitoring. The device, as seen in Figure 5.1, was placed via two electrodes in the second intercostal space. A modified exercise protocol was used to evaluate ECG changes over varying heart rates for 6 minutes (Figure 5.2). Skin was prepped and a CardioSTAT was applied while each patient was supine. An modified exercise test was devised based on previous observations that QT interval changes noted during sitting to standing, and in recovery after exercise are most useful in detecting Long QT Syndrome[93,182-184]. After one minute, patients stood for one minute, followed by two minutes walking at patient-determined normal pace. Finally, patients returned supine for two minutes.

5.3.4   Data and Statistical Analysis

CardioSTAT raw data was reviewed by trained technologists at iCentia, blinded to any descriptive factors including case/control and anthropometric data. R-R interval, QT interval, and T-peak to T-end intervals (Tpe) were calculated by verified computer algorithm for each heartbeat for the duration of the protocol. The corrected QT interval was calculated with Bazett's formula (QTc). QT prolongation was considered >460ms in females and >440 in males as per Long QT Syndrome diagnostic guidelines[141]. Further QT analyses also included correction by Hodges' formula (QTh), which was previously suggested as the most accurate

means of correction in a sample of 100 females with AN[152]. However, Bazett's formula is still most commonly used and Hodges' superiority has not been consistently shown[10].

The data was divided into three groups for comparison: AN patients, non-AN patients diagnosed with other ED, and healthy controls. Principal comparisons were conducted with AN patients vs. healthy controls. The non-AN patient data was primarily used to generate hypotheses, as this was a more heterogeneous sample. QT interval and HR measurements at baseline, maximum HR, and final recovery were used for analyses. In addition, QT intervals from healthy control HR matched to maximum AN patient HR were compared. Categorical variables were compared with χ^2 tests. The Shapiro-Wilk test was used to determine approximation of normal distribution. Normally distributed continuous variables were reported as mean ± standard deviation and compared with the student's t-test. Comparisons within groups were analyzed with a paired t-test. Nonparametric variables were expressed as median (interquartile range) and compared using Mann-Whitney U test. All statistical calculations were performed using R software, version 3.1.2 (The R Project for Statistical Computing, Vienna, Austria) and figures were made using Microsoft Excel 2016[107].

5.4   Results

The results presented are preliminary findings. To date, 17 inpatients and 14 age- and sex-matched controls have been enrolled, with processed data available in 13 inpatients and 5 healthy controls. We aim to include 30 eating disorder patients with a 1:2 patient:control ratio for manuscript publication. ECG analyses including additional time points (i.e. transition from supine to standing, etc.) will be included for publication; given the small sample size of the preliminary data, these analyses were not included at present. In addition, current comparisons to healthy controls only included the matched AN patients. Data from one healthy control was not included as it was matched to a non-AN patient, and data comparing a single control to single patients was not deemed compelling or informative.

5.4.1   Anorexia Nervosa Patients

Eleven AN inpatients (10 female) provided informed consent and completed testing (age 31±13 years, BMI 16.21±1.29 kg/m^2; Table 5.1). Median duration of illness was 25.1 months (1.8-76.0), with 6 patients (55%) having received previous formal treatment. Eight patients were prescribed psychopharmacotherapy, and one other patient was taking propranolol. Serum potassium levels were available in 8 patients; one patient was slightly hypokalemic at 3.3 mmol/L and the rest were within normal range. Four patients had a history of purging behaviour, but none had purged at least one week prior to testing.

Four patients reported a personal or family history of cardiac symptoms. One had a history of palpitations, and another had a history of chest pain. One patient had a positive family history wherein a second-degree relative died suddenly; few details were available surrounding the death, but arrhythmic SUD could be not definitively ruled out. The fourth patient survived sudden cardiac arrest four months prior to study enrolment. At the time of her arrest, the patient was engaging in purging behaviour and was severely hypokalemic (serum potassium = 2.2mmol/L); both of these were resolved at the time of evaluation.

5.4.2   Non-AN Patients

Two non-AN patients were enrolled: one female aged 57 years and one male aged 53 years (Table 1). Both were diagnosed with Other Specified Feeding and Eating Disorder and displayed subdiagnostic symptoms of binge eating disorder, without purging. As such, the BMIs of these patients were greater than those in AN (p=0.03) and considered overweight by normal standards (BMI > 25 kg/m^2). Compared to AN patients, the non-AN patients had longer duration of illness (p=0.03) but did not differ in serum potassium (p=0.64). Both non-AN patients were taking psychopharmacotherapy.

5.4.3   AN Patient Cardiovascular Evaluation

Baseline HR in AN patients was 67±11bpm which increased to a maximum 126±35bpm. From baseline to maximum HR, QTc increased (ΔQTc) 128±81ms. QTc was significantly longer at maximum HR compared to baseline and recovery (p<0.01). There was no

difference between QTc nor HR at baseline and recovery (p=0.88 and 0.23, respectively). Figure 3 shows QTc values for each participant at baseline, maximum HR, and end recovery. The QTc interval continually increased in two patients, who had the two shortest durations of disease of the cohort (0.7 and 1.5 months) but did not differ from the rest of the cohort in any other parameters.

At maximum HR, median QTc (Bazett) was dramatically abnormal (483 [435-561] ms), but QTh (Hodges) fell within normal range (355 [322-381] ms). QTc was longer than QTh (p<0.01). By Bazett's formula, 7 patients (64%) showed QTc prolongation at maximum HR, while only 1 (9%) had QTc prolongation by Hodges' formula.

Mean baseline Tpe was 81±15ms, and decreased to 74±26ms at maximum HR. At end recovery, mean Tpe increased (99±46ms) although the difference was not significant compared to baseline or maximum HR.

5.4.4 Comparison to Healthy Controls

Patients and controls were well matched (Table 2). At baseline, control HR was 59±12, which increased to a maximum 140±52bpm. Over this change, ΔQTc was 118 (91-142)ms although values did not significantly differ from baseline or from patients (p=0.13-0.80). Mean Tpe was 100±18ms at baseline, decreased to 83 ± 50ms at maximum HR, and increased to 98±14ms at end recovery. These values were not significantly different at any stage from each other or from AN patients (p=0.18-0.85). There were no differences between other ECG parameters (HR, QT, QTc, ΔQT, etc.) in patients and controls (p=0.34-0.89; Figure 4). However, as shown in Figure 4, patient QT intervals did not appear to shorten at maximum HR, and also appeared to reach lower maximum HR compared to controls although baseline and end recovery values were similar.

To adjust for differences in maximum HR reached, QTc intervals from controls at similar HR to the maximum HR achieved by their AN counterparts were analyzed (Figure 5). There

were no differences between the patients and controls: 531 (468-610) ms vs. 485 (427-543) ms, p=0.69.

5.4.5 Non-AN Patient Cardiovascular Evaluation

Both patients had similar baseline HR (61 and 65bpm) and returned to similar rates at end recovery (60 and 59bpm, respectively). Both patients showed the same pattern of relative changes, but Patient 13 showed more pronounced changes. Each patient had prolonged QTc at one time point. Patient 12's QTc interval was 471ms at maximum HR, while Patient 13 had a borderline prolonged QTc interval at end recovery (461ms).

5.5 Discussion

5.5.1 Resting QTc Interval

Current reports comparing resting QTc intervals in AN patients and controls are heterogeneous; as presented in a 2008 meta-analysis by Lesinskiene et al. and in *Chapter 4 – The QT Interval in Anorexia Nervosa: a Systematic Review and Meta-Analysis*, a clear consensus has not been reached[2]. As such, the finding in this study that baseline resting QTc intervals were not different in AN patients compared to controls is not unusual.

5.5.2 Change in QTc from Baseline to Maximum HR

The QTc increased in AN patients from baseline to maximum HR, but did not in healthy controls. Marked corrected QT interval prolongation during exercise has been previously described in congenital Long QT Syndrome patients, and is suggested as a marker of increased arrhythmic risk[182].

The magnitude of change in QTc at increased HR (ΔQTc 128±81ms) appeared to be greater than previously reported in the AN population. Padfield et al. (2016) was the only study to investigate QT changes over a gradient of HR changes in AN, and reported ΔQTc 37±28ms[75].

Two main patient population differences between the Padfield study and the current study may account for the difference. First, the Padfield study population consisted of patients deemed clinically well enough to perform complete clinical exercise testing. In contrast, the present study included deconditioned inpatients with strict activity monitoring on the ward. Secondly, this study included adult patients (age 31 ± 13 years) wherein the other was of an adolescent population (age 15.6 ± 1.9 years). Age differences in QT dynamics have been demonstrated to be maintained throughout exercise, although a meta-analysis of AN patients did not reveal any differences in QTc between two similarly aged groups (15.4 ± 1.6 vs. 25.4 ± 4.4 years)[2,185].

5.5.3 Comparison of QT Throughout Exercise to Healthy Controls

Patient QT interval trended towards being longer compared to control at elevated HR, both at maximal HR (Figure 5.4) and matched HR (Figure 5.5). As the sample size grows, this data will potentially inform arrhythmic risk assessment during exercise in the AN population. These data are similar to the findings of Padfield et al[75]. Failed QT shortening during exercise in AN patients may present a marker for arrhythmia risk as seen in congenital Long QT Syndrome[93].

5.5.4 Other ECG Modifiers and Parameters

The majority of patients were prescribed psychopharmacotherapies, which have been demonstrated to prolong the QT interval in normal-weight populations and AN case reports, but not in a cohort of AN patients as described in *Chapter 3 – Electrocardiographic Markers of Repolarization in Eating Disorders: a Case Control Study*[68,160,168,186,187]. As such, we do not believe this had a significant impact on the results although the possibility cannot be definitively ruled out.

Increased Tpe has been identified as a marker of arrhythmic risk[126,136]; interestingly, Tpe trended towards being increased in healthy controls compared to AN patients. Inclusion of more patients is warranted to clarify any differences in these populations.

5.5.5   QT Correction Formulae

The results of this study exemplify the importance of QT correction formula with elevated HR. Specifically, when correcting QT intervals at maximum HR by Bazett's formula, 64% of patients showed prolonged QT, while only 9% of patients were prolonged by Hodges' formula. These values may have clinical implications as prescription QT-altering medications and activity restrictions may be determined by the QTc interval. Further, 2/4 controls had prolonged QTc by Bazett's while none had prolonged QTc by Hodges' correction. Bazett's formula is consistently noted to be inferior to other formulae and overcorrect at higher HR, but is still the most commonly used method of QT correction in both the literature and clinical AN settings[2,9,10,152]. A clearly superior formula to replace Bazett's has not been identified, so researchers and clinicians continue to rely on this less than ideal method.

5.5.6   Future Planned Analyses

In addition to continuing enrollment and control-matching, we have begun collecting 3-month follow-up data on AN patients. Future analyses will include comparison of the follow-up data to baseline and to healthy controls. In addition, correlations of clinical characteristics (i.e. BMI, age, duration of illness) to QTc will be analyzed at baseline, maximum HR, and end recovery; at present, too few patients are enrolled to produce informative results. These analyses will be important as a single ECG change is not sufficient to stratify SUD risk, but rather should be combined with clinical presentation and concurrent ECG changes to assess risk[188]. Further, analysis of additional non-AN patient data will prompt hypotheses for future research, potentially discerning altered QT dynamics across eating disorder diagnoses.
As stated, the study aims to include 30 AN patients with follow-up and a 2:1 control:patient matched ratio. We plan to complete enrolment by October 2017.

5.6   Conclusion

The preliminary results suggest comparable ECG changes throughout exercise in AN patients; however, enlargement of the sample size may clarify potential trends observed.

Specifically, the QT interval may fail to appropriately shorten in acute AN at elevated HR, suggesting patients at increase arrhythmic risk.

5.7 Tables

Table 5.1 Clinical characteristics of AN and non-AN patients.

Characteristic	AN Patient (n=11)	Non-AN Patient (n=2)
Age (years)	31±13	55±3
BMI (kg/m^2)	16.21±1.29	28.9±5.5
Sex (% female)	91%	50%
Duration of illness (median [IQR])	25.1 (1.8-76.0) months	5-32 years
Previous treatment (n, %)	6, 55%	2, 100%
Psychopharmacotherapy(n, %)	8, 73%	2, 100%
Other cardiac medications (n, %)	1, 9%	0
Serum potassium (mmol/L)	4.0 ± 0.3 (n=8)	4.3 ± 0.7
History of purging (n, %)*	4, 36%	0

*No patients purged within 1 week of testing

Table 5.2 Demographics of patients and controls

Demographic	Matched AN Patient (n=4)	Healthy Controls (n=4)	P-value
Age	25±7	25±7	0.94
BMI (kg/m^2)	16.4±1.7	22.7±1.7	<0.01
Sex (% female)	75%	75%	1.00

5.8   Figures
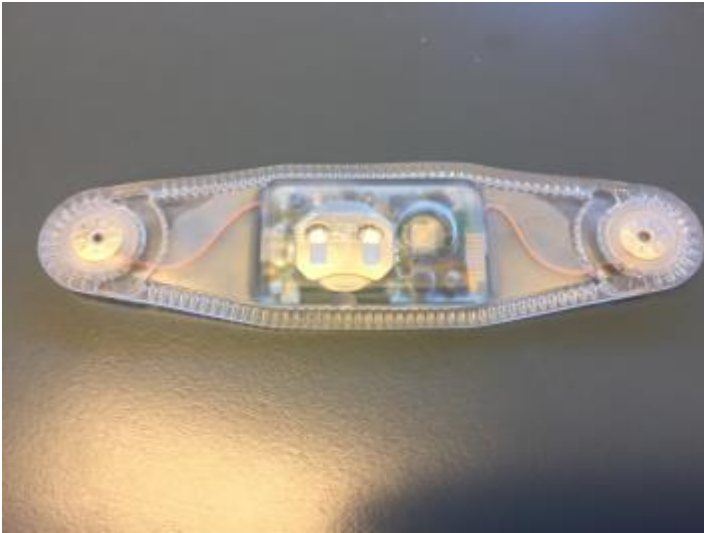
Figure 5.1 The iCentia CardioSTAT device.

The device measures 14.0x3.2x0.5cm and is attached to the patient by two electrodes.

Figure 5.2 Modified exercise protocol.

Patients completed the protocol at baseline and 3-month follow-up, while healthy controls completed the

protocol once.
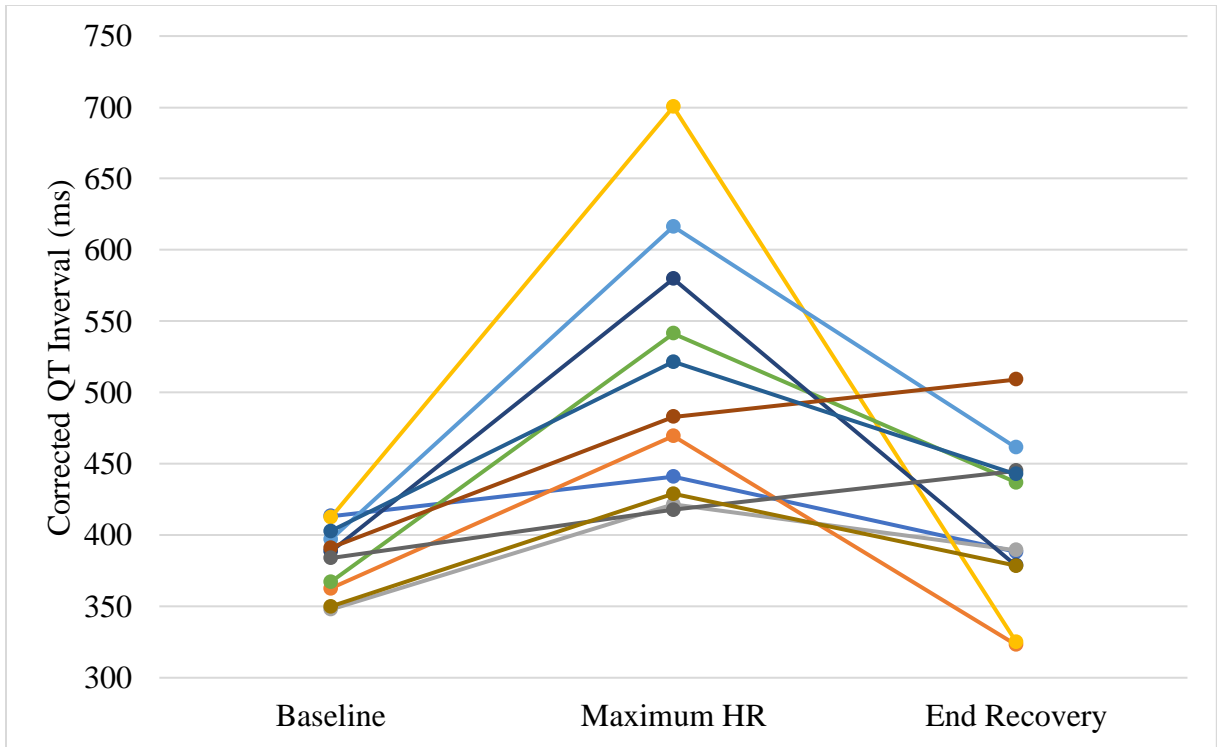
Figure 5.3 Corrected QT intervals at three time points.

QTc significantly increased at maximum HR compared to baseline (383±23ms vs. 511±91ms, p<0.01). Each line represents one AN patient.
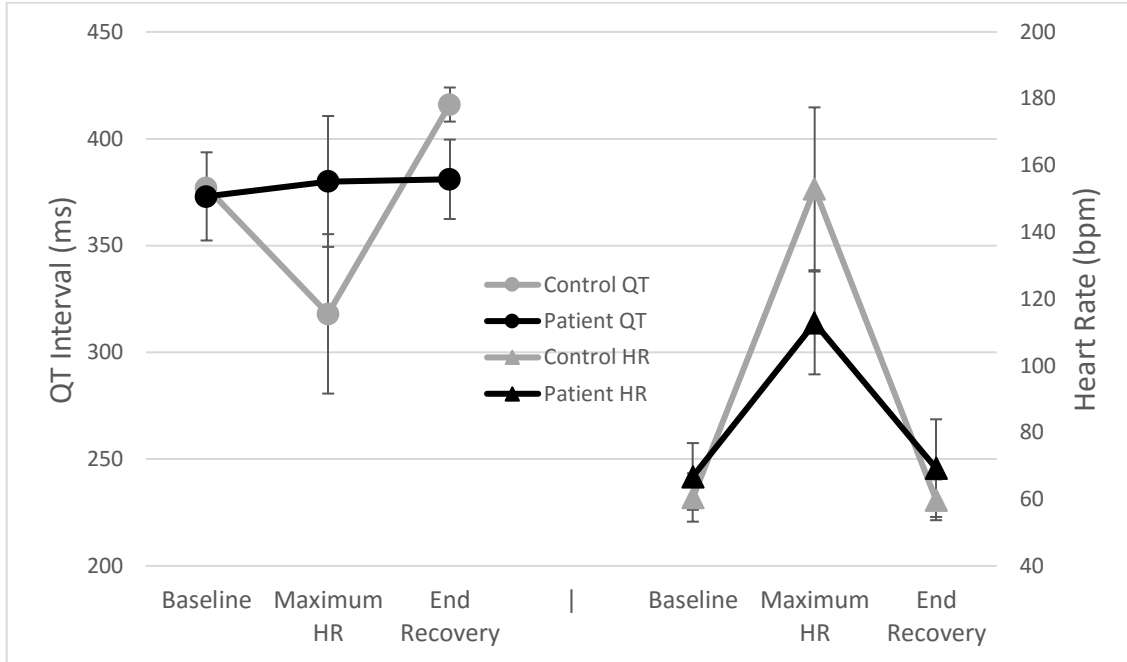
Figure 5.4 QT interval and HR

There was no difference in QT interval or HR at any stage between AN patients and matched healthy controls (p=0.13-0.8). Error bars = standard error of the mean.
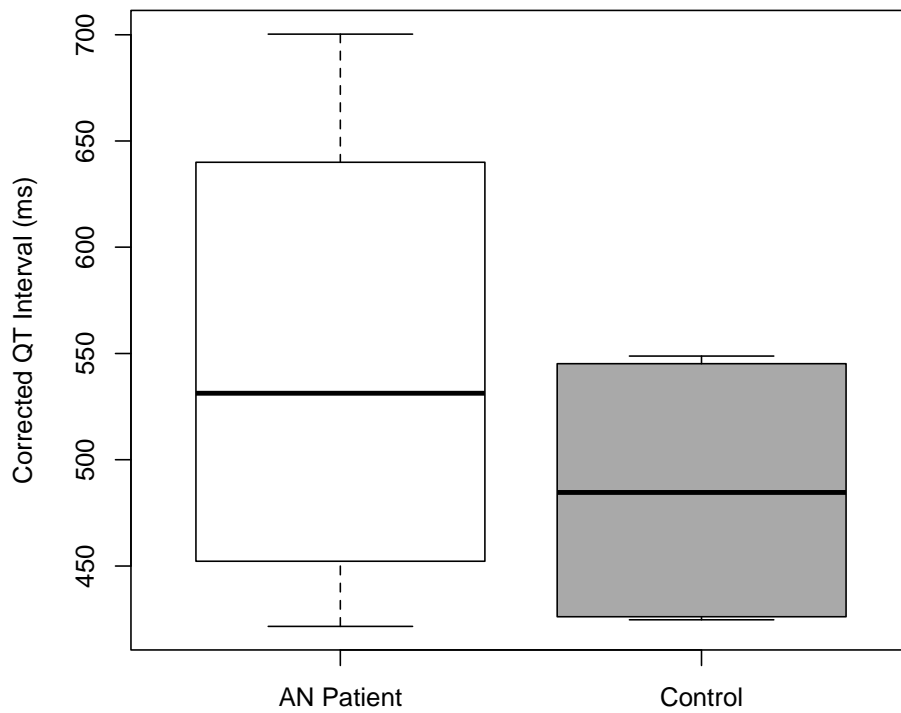
Figure 5.5 QTc of AN patients and controls at matched maximum HR.

There was no difference between corrected QT (QTc) interval in AN and controls at HR matched to the

maximum of AN patients (109 [90-126] bpm vs. 115 [90-138] bpm, p=0.49).

Chapter 6: Conclusion

6.1   Summary of Findings

6.1.1   Overarching Hypothesis One

The first hypothesis was that comprehensive cardiac testing is an effective and cost-efficient means of evaluation. The study outlined in *Chapter 2 – Cost Analysis of Patients Referred for Evaluation of Inherited Heart Rhythm Disorder* was designed to address this hypothesis. As described, the systematic cardiac evaluations revealed high diagnostic yield (77%) at a reasonable cost per patient ($1340 CAD). The remaining research of this thesis evaluated the utility of cardiac testing in the eating disorder, specifically anorexia nervosa, population; by first establishing that complex, multidisciplinary cardiac evaluations can have high diagnostic yield at costs comparable to other conditions, we established economic support for such investigations.

6.1.2   Overarching Hypothesis Two

Secondly, we hypothesized that psychopharmacotherapies will alter the ECG in the setting of AN and EDNOS/OSFED/UFED. Data presented in *Chapter 3 – Electrocardiographic Markers of Repolarization in Eating Disorders: a Case-Control Study* did not support this hypothesis. There was no difference in the corrected QT interval of patients on and off medications, or within patients across medication states. Psychopharmacotherpy may alter other aspects of the ECG in eating disorders, although we would not expect this to hold a significant effect on mortality risk as the QT interval is the most common repolarization parameter associated with sudden unexpected death.

6.1.3   Overarching Hypothesis Three

Finally, we hypothesized that cardiac repolarization in anorexia nervosa will differ from healthy controls and accepted norms at rest and during exercise.
In *Chapter 3 – Electrocardiographic Markers of Repolarization in Eating Disorder: a Case Control Study*, the observed mean corrected QT interval of eating disorder patients was shorter than in healthy controls. As discussed, this was potentially a byproduct of the

overcorrection observed using Bazett's QT correction formula at low heartrates. Nonetheless, two eating disorder patients had a borderline prolonged QTc interval (>460ms, ≤470ms), suggesting a subpopulation may be susceptible to QT prolongation. The specific abnormal T-wave morphologies observed in eating disorder patients were different than healthy controls. Morphologies commonly linked to morbidity and sudden death (i.e. inversion and flattening)

While *Chapter 4 – The QT Interval in Anorexia Nervosa: a Systematic Review and Meta-Analysis* did not conclude a difference in the resting QTc interval of AN patients compared to controls, a difference was observed in QT dispersion. The systematic review of 26 studies revealed a heterogeneous mix of methods and results, suggesting further standardized research is needed to conclusively elucidate the intricacies, if any, of repolarization in AN. However, meta-analysis of 8 studies showed elevated QT dispersion in AN patients compared to controls. In fact, greater QT dispersion was described in all but one study analyzed. QT dispersion has been independently linked to sudden death, and as such may present a more useful marker of mortality risk than resting QTc interval in this population.

Finally, the preliminary data presented in *Chapter 5 – Evaluation of the Exercise Electrocardiogram in Anorexia Nervosa* did not reveal any differences between patients and controls, although a significant increase in QTc at maximum HR in AN patients was observed. As we continue to collect data and expand this cohort, important findings regarding the QT interval during exercise and follow-up will be assessed.

6.2   Strengths and Limitations

Overall, the work of this thesis is most strengthened by the multitude of approaches taken to evaluate repolarization in eating disorders. Retrospective review, systematic analysis of the literature, and prospective assessment all failed to report incriminating evidence regarding the resting QT interval. The consistency of results observed across these methodologies suggests validity in the findings.

Given the systemic nature of AN, adjusting and accounting for all potential confounding variables is extremely difficult and is a great limitation to research. As was observed in *Chapter 4*, the risk of confounding bias is exceptionally tough to elude in this patient population. Unfortunately, observational studies are the most feasible and accurate way to assess sudden death risk, but also prove difficult to control for potential confounding variables while assessing a representative population.

6.3   Clinical Relevance and Potential Translational Impact

The combined results of this study contradict previous belief and suggest that the resting QT interval may not hold significant clinical importance in AN patients. The retrospective chart review revealed very few QT intervals in borderline prolonged range, and a meta-analysis did not reveal any difference from healthy controls. Regardless, cardiac repolarization does still appear to be altered in AN as visualized by other parameters, with changes in T-wave morphology and QT dispersion at rest, and possibly in the QT interval during exercise. The vast majority of AN patients have resting ECGs performed for clinical purposes; as such, an additional test does not need to be ordered to evaluate these parameters. Exercise testing is often performed near hospital discharge in AN patients to assess cardiac function; incorporating lower-impact testing at earlier treatment points and greater disease severity may provide clinical insight.

Translation of this research will be important to inform healthcare providers of the shift in focus regarding cardiac repolarization and associated sudden unexpected death risk. As most clinical research is founded by hypotheses developed on the wards, encouraging clinicians to evaluate repolarization markers other than the resting QT interval may spark future research and greater understanding. Although the absolute risk may be small, sudden death is such a finite tragedy that any potential reduction in this risk should be explored, especially if a test as simple as a resting ECG can be of use.

6.4   Future Directions

As the vast majority of cardiac repolarization research has focused on the resting QT interval, the most important future research direction is to explore other repolarization markers, such as T-wave morphology and QT dispersion. Given the potentially altered QT dynamics during exercise, evaluating T-wave and QT dispersion parameters in this setting may also be insightful. A longitudinal study evaluating cardiac repolarization over disease progression and remission would provide the most reliable insight into the clinical and diagnostic implications of cardiac and other parameters. Further, assessing the resting QT interval with consistent thresholds of abnormality will be important to identify a subset of patients, if any, with increased risk. Although the research in this thesis does not suggest the resting QT interval to be particularly useful as a marker of sudden death risk, other parameters have been identified and we have moved closer to preventing the tragedy of sudden death in anorexia nervosa.

References

1.   Janzen ML, Cheung C, Sanatani S, et al. Cost Analysis of Patients Referred for Inherited Heart Rhythm Disorder Evaluation. Can J Cardiol 2016.
2.   Lesinskiene S, Barkus A, Ranceva N, Dembinskas A. A meta-analysis of heart rate and QT interval alteration in anorexia nervosa. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry 2008.
3.   Sachs KV, Harnke B, Mehler PS, Krantz MJ. Cardiovascular complications of anorexia nervosa: A systematic review. Int J Eat Disord 2016;49:238-48.
4.   Galetta F, Franzoni F, Prattichizzo F, Rolla M, Santoro G, Pentimone F. Heart rate variability and left ventricular diastolic function in anorexia nervosa. 2003.
5.   Petretta M, Bonaduce D, Scalfi L, et al. Heart rate variability as a measure of autonomic nervous system function in anorexia nervosa. Clinical cardiology 1997;20:219-24.
6.   Melanson EL, Donahoo WT, Krantz MJ, Poirier P, Mehler PS. Resting and ambulatory heart rate variability in chronic anorexia nervosa. The American Journal of Cardiology 2004;94:1217-20.
7.   Krahn AD, Sanatani S, Gardner MJ, Arbour L. Inherited heart rhythm disease: negotiating the minefield for the practicing cardiologist. The Canadian journal of cardiology 2013;29:122-5.
8.   Van Asbroeck PJ, Huybrechts W, De Soir R. Case report, aetiology, and treatment of an acquired long-QT syndrome. Acta clinica Belgica 2014;69:132-4.
9.   Indik JH, Pearson EC, Fried K, Woosley RL. Bazett and Fridericia QT correction formulas interfere with measurement of drug-induced changes in QT interval. Heart rhythm : the official journal of the Heart Rhythm Society 2006;3:1003-7.
10.   Vandenberk B, Vandael E, Robyns T, et al. Which QT Correction Formulae to Use for QT Monitoring? Journal of the American Heart Association 2016;5.
11.   Vittoria Matassini M, Krahn AD, Gardner M, et al. Evolution of clinical diagnosis in patients presenting with unexplained cardiac arrest or syncope due to polymorphic ventricular tachycardia. Heart rhythm : the official journal of the Heart Rhythm Society 2014;11:274-81.
12.   Herman AR, Cheung C, Gerull B, et al. Outcome of Apparently Unexplained Cardiac Arrest: Results From Investigation and Follow-Up of the Prospective Cardiac Arrest Survivors With Preserved Ejection Fraction Registry. Circulation Arrhythmia and electrophysiology 2016;9:e003619.
13.   Papadopoulos FC, Ekbom A, Brandt L, Ekselius L. Excess mortality, causes of death and prognostic factors in anorexia nervosa. The British journal of psychiatry : the journal of mental science 2009;194:10-7.
14.   Meczekalski B, Podfigurna-Stopa A, Katulski K. Long-term consequences of anorexia nervosa. Maturitas 2013;75:215-20.
15.   American Psychiatric A. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, D.C.: American Psychiatric Association; 2013.
16.   American Psychiatric A. Diagnostic and Statistical Manual of Mental Disorders—Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Assocation; 2000.

17.   Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 1970;126:983-7.

18.   Zerwas S, Larsen JT, Petersen L, Thornton LM, Mortensen PB, Bulik CM. The incidence of eating disorders in a Danish register study: Associations with suicide risk and mortality. Journal of psychiatric research 2015;65:16-22.

19.   Smink FR, van Hoeken D, Donker GA, Susser ES, Oldehinkel AJ, Hoek HW. Three decades of eating disorders in Dutch primary care: decreasing incidence of bulimia nervosa but not of anorexia nervosa. Psychological medicine 2016;46:1189-96.

20.   Keski-Rahkonen A, Mustelin L. Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences, and risk factors. Curr Opin Psychiatry 2016;29:340-5.

21.   van Son GE, van Hoeken D, Bartelds AI, van Furth EF, Hoek HW. Time trends in the incidence of eating disorders: a primary care study in the Netherlands. Int J Eat Disord 2006;39:565-9.

22.   Smink FR, van Hoeken D, Hoek HW. Epidemiology of eating disorders: incidence, prevalence and mortality rates. Current psychiatry reports 2012;14:406-14.

23.   Stice E, Marti CN, Rohde P. Prevalence, incidence, impairment, and course of the proposed DSM-5 eating disorder diagnoses in an 8-year prospective community study of young women. Journal of abnormal psychology 2013;122:445-57.

24.   Bartholdy S, Allen K, Hodsoll J, et al. Identifying disordered eating behaviours in adolescents: how do parent and adolescent reports differ by sex and age? Eur Child Adolesc Psychiatry 2017.

25.   Smink FR, van Hoeken D, Oldehinkel AJ, Hoek HW. Prevalence and severity of DSM-5 eating disorders in a community cohort of adolescents. The International journal of eating disorders 2014;47:610-9.

26.   Bulik CM, Sullivan PF, Tozzi F, Furberg H, Lichtenstein P, Pedersen NL. Prevalence, heritability, and prospective risk factors for anorexia nervosa. Archives of general psychiatry 2006;63:305-12.

27.   Vo M, Accurso EC, Goldschmidt AB, Le Grange D. The Impact of DSM-5 on Eating Disorder Diagnoses. Int J Eat Disord 2016.

28.   Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. Current opinion in psychiatry 2006;19:389-94.

29.   Sweeting H, Walker L, MacLean A, Patterson C, Raisanen U, Hunt K. Prevalence of eating disorders in males: a review of rates reported in academic research and UK mass media. International journal of men's health 2015;14.

30.   Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. Archives of general psychiatry 2011;68:724-31.

31.   Di Cola G, Jacoangeli F, Jacoangeli F, Lombardo M, Iellamo F. Cardiovascular disorders in anorexia nervosa and potential therapeutic targets. Internal and emergency medicine 2014;9:717-21.

32.   Isner JM, Roberts WC, Heymsfield SB, Yager J. Anorexia nervosa and sudden death. Annals of Internal Medicine 1985;102:49-52.

33.   Thomas JJ, Roberto CA, Brownell KD. Eighty-five per cent of what? Discrepancies in the weight cut-off for anorexia nervosa substantially affect the prevalence of underweight. Psychological medicine 2009;39:833-43.

34.   Arcelus J, Witcomb GL, Mitchell A. Prevalence of eating disorders amongst dancers: a systemic review and meta-analysis. Eur Eat Disord Rev 2014;22:92-101.

35.   Pike KM, Hilbert A, Wilfley DE, et al. Toward an understanding of risk factors for anorexia nervosa: a case-control study. Psychological medicine 2008;38:1443-53.

36.   Record KL, Austin SB. "Paris Thin": A Call to Regulate Life-Threatening Starvation of Runway Models in the US Fashion Industry. American journal of public health 2016;106:205-6.

37.   Treasure JL, Wack ER, Roberts ME. Models as a high-risk group: the health implications of a size zero culture. Br J Psychiatry 2008;192:243-4.

38.   Pike KM, Dunne PE. The rise of eating disorders in Asia: a review. Journal of eating disorders 2015;3:33.

39.   Pike KM, Borovoy A. The rise of eating disorders in Japan: issues of culture and limitations of the model of "westernization". Culture, medicine and psychiatry 2004;28:493-531.

40.   Guo Y, Wei Z, Keating BJ, Hakonarson H. Machine learning derived risk prediction of anorexia nervosa. BMC medical genomics 2016;9:4.

41.   Strober M, Freeman R, Lampert C, Diamond J, Kaye W. Controlled family study of anorexia nervosa and bulimia nervosa: evidence of shared liability and transmission of partial syndromes. Am J Psychiatry 2000;157:393-401.

42.   Klump KL, Suisman JL, Burt SA, McGue M, Iacono WG. Genetic and environmental influences on disordered eating: An adoption study. Journal of abnormal psychology 2009;118:797-805.

43.   Klump KL, Miller KB, Keel PK, McGue M, Iacono WG. Genetic and environmental influences on anorexia nervosa syndromes in a population-based twin sample. Psychological medicine 2001;31:737-40.

44.   Fairburn CG, Cooper Z, Doll HA, Welch SL. Risk factors for anorexia nervosa: three integrated case-control comparisons. Archives of general psychiatry 1999;56:468-76.

45.   Fairburn CG, Welch SL, Doll HA, Davies BA, O'Connor ME. Risk factors for bulimia nervosa. A community-based case-control study. Archives of general psychiatry 1997;54:509-17.

46.   Fairburn CG, Doll HA, Welch SL, Hay PJ, Davies BA, O'Connor ME. Risk factors for binge eating disorder: a community-based, case-control study. Archives of general psychiatry 1998;55:425-32.

47.   Karwautz A, Rabe-Hesketh S, Hu X, et al. Individual-specific risk factors for anorexia nervosa: a pilot study using a discordant sister-pair design. Psychological medicine 2001;31:317-29.

48.   Lavender JM, Mason TB, Utzinger LM, et al. Examining affect and perfectionism in relation to eating disorder symptoms among women with anorexia nervosa. Psychiatry Res 2016;241:267-72.

49.   Lazarevic J, Batinic B, Vukosavljevic-Gvozden T. Risk factors and the prevalence of anorexia nervosa among female students in Serbia. Vojnosanit Pregl 2016;73:34-41.

50.   Norring CE, Sohlberg SS. Outcome, recovery, relapse and mortality across six years in patients with clinical eating disorders. Acta psychiatrica Scandinavica 1993;87:437-44.
51.   Theander S. Outcome and prognosis in anorexia nervosa and bulimia: some results of previous investigations, compared with those of a Swedish long-term study. J Psychiatr Res 1985;19:493-508.
52.   Lowe B, Zipfel S, Buchholz C, Dupont Y, Reas DL, Herzog W. Long-term outcome of anorexia nervosa in a prospective 21-year follow-up study. Psychological medicine 2001;31:881-90.
53.   Herzog DB, Dorer DJ, Keel PK, et al. Recovery and relapse in anorexia and bulimia nervosa: a 7.5-year follow-up study. J Am Acad Child Adolesc Psychiatry 1999;38:829-37.
54.   Morris J, Twaddle S. Anorexia nervosa. BMJ (Clinical research ed) 2007;334:894-8.
55.   Shamim T, Golden NH, Arden M, Filiberto L, Shenker IR. Resolution of vital sign instability: an objective measure of medical stability in anorexia nervosa. The Journal of adolescent health : official publication of the Society for Adolescent Medicine 2003;32:73-7.
56.   Mont L, Castro J, Herreros B, et al. Reversibility of cardiac abnormalities in adolescents with anorexia nervosa after weight recovery. 2003.
57.   Lachish M, Stein D, Kaplan Z, et al. Irreversibility of cardiac autonomic dysfunction in female adolescents diagnosed with anorexia nervosa after short- and long-term weight gain. 2009.
58.   Abed J, Judeh H, Abed E, Kim M, Arabelo H, Gurunathan R. "fixing a heart": The game of electrolytes in anorexia nervosa.
59.   Nicholls D, Hudson L, Mahomed F. Managing anorexia nervosa. Archives of disease in childhood 2011;96:977-82.
60.   Van Son GE, Quek R, Focteloo AJ, Van Furth EF. Criteria for admitting patients with anorexia nervosa as inpatients to a general hospital; survey among internists. [Dutch].
61.   Garber AK, Sawyer SM, Golden NH, et al. A systematic review of approaches to refeeding in patients with anorexia nervosa. Int J Eat Disord 2016;49:293-310.
62.   Hofer M, Pozzi A, Joray M, et al. Safe refeeding management of anorexia nervosa inpatients: an evidence-based protocol. Nutrition (Burbank, Los Angeles County, Calif) 2014;30:524-30.
63.   Boateng AA, Sriram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. Nutrition (Burbank, Los Angeles County, Calif) 2010;26:156-67.
64.   O'Connor G, Nicholls D, Hudson L, Singhal A. Refeeding Low Weight Hospitalized Adolescents with Anorexia Nervosa: A Multicenter Randomized Controlled Trial. 2016.
65.   Godart N, Radon L, Curt F, et al. Mood disorders in eating disorder patients: Prevalence and chronology of ONSET. Journal of affective disorders 2015;185:115-22.
66.   Mehler-Wex C, Romanos M, Kirchheiner J, Schulze UM. Atypical antipsychotics in severe anorexia nervosa in children and adolescents--review and case reports. European eating disorders review : the journal of the Eating Disorders Association 2008;16:100-8.
67.   Gordon M, Melvin G. Selective serotonin re-uptake inhibitors--a review of the side effects in adolescents. Australian Family Physician 2013;42:620-3.
68.   Hagman J, Gralla J, Sigel E, et al. A double-blind, placebo-controlled study of risperidone for the treatment of adolescents and young adults with anorexia nervosa: A pilot study. 2011;50.

69.   Aigner M, Treasure J, Kaye W, Kasper S, Disorders WTFOE. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry 2011;12:400-43.

70.   National Collaborating Centre for Mental H. National Institute for Health and Clinical Excellence: Guidance. Eating Disorders: Core Interventions in the Treatment and Management of Anorexia Nervosa, Bulimia Nervosa and Related Eating Disorders. Leicester (UK): British Psychological Society (UK)

The British Psychological Society & The Royal College of Psychiatrists.; 2004.

71.   Fazeli PK, Calder GL, Miller KK, et al. Psychotropic medication use in anorexia nervosa between 1997 and 2009. Int J Eat Disord 2012;45:970-6.

72.   Garner DM, Anderson ML, Keiper CD, Whynott R, Parker L. Psychotropic medications in adult and adolescent eating disorders: clinical practice versus evidence-based recommendations. Eat Weight Disord 2016;21:395-402.

73.   Docx MK, Gewillig M, Simons A, et al. Pericardial effusions in adolescent girls with anorexia nervosa: clinical course and risk factors. Eat Disord 2010;18:218-25.

74.   Romano C, Chinali M, Pasanisi F, et al. Reduced hemodynamic load and cardiac hypotrophy in patients with anorexia nervosa. The American journal of clinical nutrition 2003;77:308-12.

75.   Padfield GJ, Escudero CA, DeSouza AM, et al. Characterization of Myocardial Repolarization Reserve in Adolescent Females With Anorexia Nervosa. Circulation 2016;133:557-65.

76.   Gottdiener JS, Gross HA, Henry WL, Borer JS, Ebert MH. Effects of self-induced starvation on cardiac size and function in anorexia nervosa. Circulation 1978;58:425-33.

77.   McLoughlin DM, Spargo E, Wassif WS, et al. Structural and functional changes in skeletal muscle in anorexia nervosa. Acta neuropathologica 1998;95:632-40.

78.   Russell DM, Prendergast PJ, Darby PL, Garfinkel PE, Whitwell J, Jeejeebhoy KN. A comparison between muscle function and body composition in anorexia nervosa: the effect of refeeding. The American journal of clinical nutrition 1983;38:229-37.

79.   Yahalom M, Spitz M, Sandler L, Heno N, Roguin N, Turgeman Y. The significance of bradycardia in anorexia nervosa. 2013.

80.   Campbell K, Peebles R. Eating disorders in children and adolescents: state of the art review. Pediatrics 2014;134:582-92.

81.   Muller MJ, Enderle J, Pourhassan M, et al. Metabolic adaptation to caloric restriction and subsequent refeeding: the Minnesota Starvation Experiment revisited. The American journal of clinical nutrition 2015;102:807-19.

82.   Billeci L, Tartarisco G, Brunori E, et al. The role of wearable sensors and wireless technologies for the assessment of heart rate variability in anorexia nervosa. Eating and weight disorders : EWD 2015;20:23-31.

83.   Swenne I, Larsson PT. Heart risk associated with weight loss in anorexia nervosa and eating disorders: risk factors for QTc interval prolongation and dispersion. Acta Paediatrica (Oslo, Norway : 1992) 1999;88:304-9.

84.   Ono T, Kasaoka S, Fujita M, et al. Complete recovery from severe myocardial dysfunction in a patient with anorexia nervosa.

85.   Roche F, Barthelemy JC, Mayaud N, et al. Refeeding normalizes the QT rate dependence of female anorexic patients. The American Journal of Cardiology 2005;95:277-80.

86.   Facchini M, Sala L, Malfatto G, Bragato R, Redaelli G, Invitti C. Low-K+ dependent QT prolongation and risk for ventricular arrhythmia in anorexia nervosa. International journal of cardiology 2006;106:170-6.

87.   Johnson JN, Ackerman MJ. QTc: how long is too long? British journal of sports medicine 2009;43:657-62.

88.   Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. British heart journal 1990;63:342-4.

89.   Galetta F, Franzoni F, Cupisti A, Belliti D, Prattichizzo F, Rolla M. QT interval dispersion in young women with anorexia nervosa. 2002.

90.   Epstein AE, Dimarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: executive summary. Heart rhythm : the official journal of the Heart Rhythm Society 2008;5:934-55.

91.   Priori SG, Wilde AA, Horie M, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Heart rhythm : the official journal of the Heart Rhythm Society 2013;10:e85-108.

92.   Hofman N, Tan HL, Alders M, et al. Yield of molecular and clinical testing for arrhythmia syndromes: report of 15 years' experience. Circulation 2013;128:1513-21.

93.   Sy RW, Chattha IS, Klein GJ, et al. Repolarization dynamics during exercise discriminate between LQT1 and LQT2 genotypes. Journal of cardiovascular electrophysiology 2010;21:1242-6.

94.   Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart rhythm : the official journal of the Heart Rhythm Society 2011;8:1308-39.

95.   Gollob MH, Blier L, Brugada R, et al. Recommendations for the use of genetic testing in the clinical evaluation of inherited cardiac arrhythmias associated with sudden cardiac death: Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position paper. The Canadian journal of cardiology 2011;27:232-45.

96.   Krahn AD, Healey JS, Chauhan V, et al. Systematic assessment of patients with unexplained cardiac arrest: Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER). Circulation 2009;120:278-85.

97.   Bai R, Napolitano C, Bloise R, Monteforte N, Priori SG. Yield of genetic screening in inherited cardiac channelopathies: how to prioritize access to genetic testing. CirculationArrhythmia and electrophysiology 2009;2:6-15.

98.   Chockalingam P, Wilde AA. Inherited arrhythmia syndromes leading to sudden cardiac death in the young: a global update and an Indian perspective. Indian heart journal 2014;66 Suppl 1:S49-57.

99.   Janzen M, Sanatani S, Gibbs KA, et al. Inherited heart rhythm disorders: Diagnostic dilemmas after the sudden death of a young family member. Journal of Nursing Education and Practice 2014;4:225-33.

100. Krahn AD, Healey JS, Chauhan VS, et al. Epinephrine infusion in the evaluation of unexplained cardiac arrest and familial sudden death: from the cardiac arrest survivors with preserved Ejection Fraction Registry. CirculationArrhythmia and electrophysiology 2012;5:933-40.

101. Somani R, Krahn AD, Healey JS, et al. Procainamide infusion in the evaluation of unexplained cardiac arrest: from the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER). Heart rhythm : the official journal of the Heart Rhythm Society 2014;11:1047-54.

102. Adler A, Sadek MM, Chan AY, et al. Patient Outcomes From a Specialized Inherited Arrhythmia Clinic. CirculationArrhythmia and electrophysiology 2016;9:10.1161/CIRCEP.115.003440.

103. Krahn AD, Healey JS, Simpson CS, et al. Sentinel symptoms in patients with unexplained cardiac arrest: from the cardiac arrest survivors with preserved ejection fraction registry (CASPER). Journal of cardiovascular electrophysiology 2012;23:60-6.

104. Bennett MT, Gula LJ, Klein GJ, et al. Effect of beta-blockers on QT dynamics in the long QT syndrome: measuring the benefit. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2014;16:1847-51.

105. Morales A, Hershberger RE. The Rationale and Timing of Molecular Genetic Testing for Dilated Cardiomyopathy. The Canadian journal of cardiology 2015;31:1309-12.

106. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in medicine : official journal of the American College of Medical Genetics 2015;17:405-24.

107. Team RC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2014.

108. Bennett M, Parkash R, Nery P, et al. CCS/CHRS 2016 Implantable Cardioverter-Defibrillator (ICD) Guidelines. Canadian Journal of Cardiology 2016.

109. Spoonamore KG, Ware SM. Genetic testing and genetic counseling in patients with sudden death risk due to heritable arrhythmias. Heart rhythm : the official journal of the Heart Rhythm Society 2015.

110. Vavolizza RD, Kalia I, Erskine Aaron K, et al. Disclosing Genetic Information to Family Members About Inherited Cardiac Arrhythmias: An Obligation or a Choice? Journal of genetic counseling 2015;24:608-15.

111. Krahn AD, Klein GJ, Yee R, Hoch JS, Skanes AC. Cost implications of testing strategy in patients with syncope: randomized assessment of syncope trial. Journal of the American College of Cardiology 2003;42:495-501.

112. Shaw LJ, Heller GV, Travin MI, et al. Cost analysis of diagnostic testing for coronary artery disease in women with stable chest pain. Economics of Noninvasive Diagnosis (END) Study Group. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 1999;6:559-69.

113. Sheikh A, Patel NJ, Nalluri N, et al. Trends in hospitalization for atrial fibrillation: epidemiology, cost, and implications for the future. Progress in cardiovascular diseases 2015;58:105-16.

114.   Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. CirculationCardiovascular quality and outcomes 2011;4:313-20.

115.   Phillips KA, Ackerman MJ, Sakowski J, Berul CI. Cost-effectiveness analysis of genetic testing for familial long QT syndrome in symptomatic index cases. Heart rhythm : the official journal of the Heart Rhythm Society 2005;2:1294-300.

116.   Benito B, Sarkozy A, Mont L, et al. Gender differences in clinical manifestations of Brugada syndrome. Journal of the American College of Cardiology 2008;52:1567-73.

117.   Cerrone M, Cummings S, Alansari T, Priori SG. A clinical approach to inherited arrhythmias. CirculationCardiovascular genetics 2012;5:581-90.

118.   McNally E, MacLeod H, Dellefave-Castillo L. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews(R). Seattle (WA): University of Washington, Seattle; 1993.

119.   Napolitano C, Schwartz PJ, Brown AM, et al. Evidence for a cardiac ion channel mutation underlying drug-induced QT prolongation and life-threatening arrhythmias. J Cardiovasc Electrophysiol 2000;11:691-6.

120.   Yang P, Kanki H, Drolet B, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation 2002;105:1943-8.

121.   Striegel-Moore RH, Leslie D, Petrill SA, Garvin V, Rosenheck RA. One-year use and cost of inpatient and outpatient services among female and male patients with an eating disorder: evidence from a national database of health insurance claims. Int J Eat Disord 2000;27:381-9.

122.   Nannenberg EA, Sijbrands EJ, Dijksman LM, et al. Mortality of inherited arrhythmia syndromes: insight into their natural history. Circulation Cardiovascular genetics 2012;5:183-9.

123.   Laukkanen JA, Di Angelantonio E, Khan H, Kurl S, Ronkainen K, Rautaharju P. T-wave inversion, QRS duration, and QRS/T angle as electrocardiographic predictors of the risk for sudden cardiac death. Am J Cardiol 2014;113:1178-83.

124.   Vanderdonckt O, Lambert M, Cornejo Montero M, Boland B, Brohet C. The 12-lead electrocardiogram in anorexia nervosa: A report of 2 cases followed by a retrospective study. 2001.

125.   Mohee K, Kucharska-Pietura K, Karthigeyan A, Naqvi A. Diagnostic and treatment dilemmas of persistent chronic hypokalaemia in a patient with anorexia nervosa: a case report. J Med Case Rep 2014;8:294.

126.   Morin DP, Saad MN, Shams OF, et al. Relationships between the T-peak to T-end interval, ventricular tachyarrhythmia, and death in left ventricular systolic dysfunction. Europace 2012;14:1172-9.

127.   Panagiotopoulos C, McCrindle BW, Hick K, Katzman DK. Electrocardiographic findings in adolescents with eating disorders. Pediatrics 2000;105:1100-5.

128.   Biadi O, Rossini R, Musumeci G, et al. Cardiopulmonary exercise test in young women affected by anorexia nervosa. 2001.

129.   Ertugrul I, Akgul S, Derman O, Karagoz T, Kanbur N. Increased P-Wave Dispersion a Risk for Atrial Fibrillation in Adolescents With Anorexia Nervosa. Eating disorders 2015:1-9.

130. Olivares JL, Vazquez M, Fleta J, Moreno LA, Perez-Gonzalez JM, Bueno M. Cardiac findings in adolescents with anorexia nervosa at diagnosis and after weight restoration. 2005.
131. Calabro MP, Barberi I, La Mazza A, et al. Bifid T waves in leads V2 and V3 in children: a normal variant. Italian journal of pediatrics 2009;35:17.
132. Dickinson DF. The normal ECG in childhood and adolescence. Heart 2005;91:1626-30.
133. Bjornstad H, Storstein L, Meen HD, Hals O. Electrocardiographic findings of repolarization in athletic students and control subjects. Cardiology 1994;84:51-60.
134. Dilaveris P, Gialafos E, Poloniecki J, et al. Changes of the T-wave amplitude and angle: an early marker of altered ventricular repolarization in hypertension. Clin Cardiol 2000;23:600-6.
135. Shibuya-Tayoshi S, Taniguchi T, Moriya C, et al. Reversible left ventricular dysfunction complicating eating disorder [2]. General hospital psychiatry 2005;28:178-82.
136. Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. Circulation Arrhythmia and electrophysiology 2011;4:441-7.
137. Mozos I, Serban C. The relation between QT interval and T-wave variables in hypertensive patients. Journal of pharmacy & bioallied sciences 2011;3:339-44.
138. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation 1998;98:1928-36.
139. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
140. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
141. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. Circulation 1993;88:782-4.
142. Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. Circulation 2011;124:2181-4.
143. Schwartz PJ. The congenital long QT syndromes from genotype to phenotype: clinical implications. Journal of internal medicine 2006;259:39-47.
144. Viswanathan M, Berkman ND. Development of the RTI item bank on risk of bias and precision of observational studies. Journal of clinical epidemiology 2012;65:163-78.
145. Viswanathan M, Berkman ND, Dryden DM, Hartling L. AHRQ Methods for Effective Health Care. Assessing Risk of Bias and Confounding in Observational Studies of Interventions or Exposures: Further Development of the RTI Item Bank. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.
146. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
147. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
148. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
149. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.

150. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
151. Peebles R, Hardy KK, Wilson JL, Lock JD. Are diagnostic criteria for eating disorders markers of medical severity? 2010.
152. Walter C, Rottler E, von Wietersheim J, Cuntz U. QT-correction formulae and arrhythmogenic risk in female patients with anorexia nervosa. International journal of cardiology 2015;187:302-3.
153. Franzoni F, Mataloni E, Femia R, Galetta F. Effect of oral potassium supplementation on QT dispersion in anorexia nervosa. 2002.
154. Ulger Z, Gurses D, Ozyurek AR, Arikan C, Levent E, Aydogdu S. Follow-up of cardiac abnormalities in female adolescents with anorexia nervosa after refeeding. 2006.
155. Krantz MJ, Donahoo WT, Melanson EL, Mehler PS. QT interval dispersion and resting metabolic rate in chronic anorexia nervosa. 2005.
156. Luo S, Michler K, Johnston P, Macfarlane PW. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. J Electrocardiol 2004;37 Suppl:81-90.
157. Kuo CS, Atarashi H, Reddy CP, Surawicz B. Dispersion of ventricular repolarization and arrhythmia: study of two consecutive ventricular premature complexes. Circulation 1985;72:370-6.
158. Claudio Bde Q, Costa MA, Penna F, et al. Impact of psychotropic drugs on QT interval dispersion in adult patients. Arquivos brasileiros de cardiologia 2014;102:465-72.
159. Kelmanson IA. High anxiety in clinically healthy patients and increased QT dispersion: a meta-analysis. European journal of preventive cardiology 2014;21:1568-74.
160. Ucok A, Gaebel W. Side effects of atypical antipsychotics: a brief overview. World psychiatry : official journal of the World Psychiatric Association (WPA) 2008;7:58-62.
161. Aytemir K, Ozer N, Aksoyek S, Ozcebe O, Kabakci G, Oto A. Increased QT dispersion in the absence of QT prolongation in patients with Behcet's disease and ventricular arrhythmias. Int J Cardiol 1998;67:171-5.
162. Kors JA, van Herpen G, van Bemmel JH. QT dispersion as an attribute of T-loop morphology. Circulation 1999;99:1458-63.
163. Akdemir D, Sahin M, Sinir H, Derman O, Pehlivanturk B, Celiker A. Anorexia nervosa in a young, sportive male with severe bradycardia. 2010.
164. McCallum K, Bermudez O, Ohlemeyer C, Tyson E, Portilla M, Ferdman B. How should the clinician evaluate and manage the cardiovascular complications of anorexia nervosa? Eating disorders 2006;14:73-80.
165. Root TL, Pinheiro AP, Thornton L, et al. Substance use disorders in women with anorexia nervosa. Int J Eat Disord 2010;43:14-21.
166. Neumarker KJ. Mortality and sudden death in anorexia nervosa. Int J Eat Disord 1997;21:205-12.
167. DiVasta AD, Walls CE, Feldman HA, et al. Malnutrition and hemodynamic status in adolescents hospitalized for anorexia nervosa. Arch Pediatr Adolesc Med 2010;164:706-13.
168. Krantz MJ, Sabel AL, Sagar U, et al. Factors influencing QT prolongation in patients hospitalized with severe anorexia nervosa. General hospital psychiatry 2012;34:173-7.

169.	Nahshoni E, Weizman A, Yaroslavsky A, Toledano A, Sulkes J, Stein D. Alterations in QT dispersion in the surface electrocardiogram of female adolescents diagnosed with restricting-type anorexia nervosa. 2007.

170.	Nussinovitch M, Gur E, Kaminer K, Volovitz B, Nussinovitch N, Nussinovitch U. QT variability among weight-restored patients with anorexia nervosa. 2012.

171.	Olivares JL, Vazquez M, Fleta J, Moreno LA, Perez-Gonzalez JM, Bueno M. Cardiac findings in adolescents with anorexia nervosa at diagnosis and after weight restoration. European journal of pediatrics 2005;164:383-6.

172.	Roche F, Estour B, Kadem M, et al. Alteration of the QT rate dependence in anorexia nervosa. 2004.

173.	Takimoto Y, Yoshiuchi K, Akabayashi A. Effect of mood states on QT interval and QT dispersion in eating disorder patients. 2008.

174.	Vazquez M, Olivares Lopez JL, Fleta J, Lacambra I, Gonzalez M. Cardiac disorders in young women with anorexia nervosa. [Spanish]. 2003.

175.	Bergh C, Callmar M, Danemar S, et al. Effective treatment of eating disorders: Results at multiple sites. Behavioral neuroscience 2013;127:878-89.

176.	Grilo CM, Pagano ME, Stout RL, et al. Stressful life events predict eating disorder relapse following remission: six-year prospective outcomes. Int J Eat Disord 2012;45:185-92.

177.	American Psychiatric A. Feeding and Eating Disorders. Diagnostic and statistical manual of mental disorders: DSM-5. Arlington, VA2013.

178.	Koschke M, Boettger MK, Macholdt C, et al. Increased QT variability in patients with anorexia nervosa--an indicator for increased cardiac mortality? The International journal of eating disorders 2010;43:743-50.

179.	Ng LW, Ng DP, Wong WP. Is supervised exercise training safe in patients with anorexia nervosa? A meta-analysis. Physiotherapy 2013;99:1-11.

180.	Nahshoni E, Yaroslavsky A, Varticovschi P, Weizman A, Stein D. Alterations in QT dispersion in the surface electrocardiogram of female adolescent inpatients diagnosed with bulimia nervosa. Comprehensive psychiatry 2010;51:406-11.

181.	van Rijn CA. [Anorexia nervosa and bulimia nervosa. IIi. Somatic complications of purging]. Nederlands tijdschrift voor geneeskunde 1998;142:1867-9.

182.	Wong JA, Gula LJ, Klein GJ, Yee R, Skanes AC, Krahn AD. Utility of treadmill testing in identification and genotype prediction in long-QT syndrome. Circulation Arrhythmia and electrophysiology 2010;3:120-5.

183.	Viskin S, Postema PG, Bhuiyan ZA, et al. The response of the QT interval to the brief tachycardia provoked by standing: a bedside test for diagnosing long QT syndrome. J Am Coll Cardiol 2010;55:1955-61.

184.	Walker BD, Krahn AD, Klein GJ, et al. Effect of change in posture and exercise on repolarization in patients with long QT syndrome with HERG channel mutations. Can J Cardiol 2005;21:33-8.

185.	Mayuga KA, Parker M, Sukthanker ND, Perlowski A, Schwartz JB, Kadish AH. Effects of age and gender on the QT response to exercise. Am J Cardiol 2001;87:163-7.

186.	Funk KA, Bostwick JR. A comparison of the risk of QT prolongation among SSRIs. The Annals of Pharmacotherapy 2013;47:1330-41.

187.	Ritchie B, Norris ML. QTc prolongation associated with atypical antipsychotic use in the treatment of adolescent-onset anorexia nervosa. 2009.

188.   Abdelghani SA, Rosenthal TM, Morin DP. Surface Electrocardiogram Predictors of Sudden Cardiac Arrest. The Ochsner journal 2016;16:280-9.

Appendices

Appendix A Cost Analysis Supplemental Materials

A.1   Definitions of the Most Common IHRD Diagnoses.

IHRD Diagnosis	Common Symptomology Circumstances (Syncope, SCA, SUD)	ECG/Clinical Testing Hallmarks	Number of Patients in Cohort with Diagnosis [any strength]
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	Occasionally exercise (no typical circumstance)	Inverted T-waves in anterior precordial leads on ECG Right ventricular fat infiltration/scarring on MRI See 2010 Task Force Criteria	96 (15%)
Brugada Syndrome (BrS)	Sleep/rest, febrile	ST elevation in anterior precordial leads on ECG, especially with high lead placement Abnormal SAECG Positive procainamide challenge	99 (16%)
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)	Exercise, excitable state	Irregular polymorphic ventricular tachycardia on exercise stress test	20 (3%)
Long QT Syndrome (LQTS)	Exercise, sudden excitement/auditory stimulus, swimming, QT prolonging drugs	Prolonged QT interval on ECG Impaired QT interval response on exercise stress test/epinephrine challenge	103 (17%)

A.2   Discharges from Inherited Arrhythmia Clinic

The majority of discharges were due to patients deemed unaffected by IHRD (73%). Both patient-decided reasons contributed to 13% of discharges and follow-up with other caregivers comprised 12%.

A.3   Pre- and Post-Referral Test Distribution
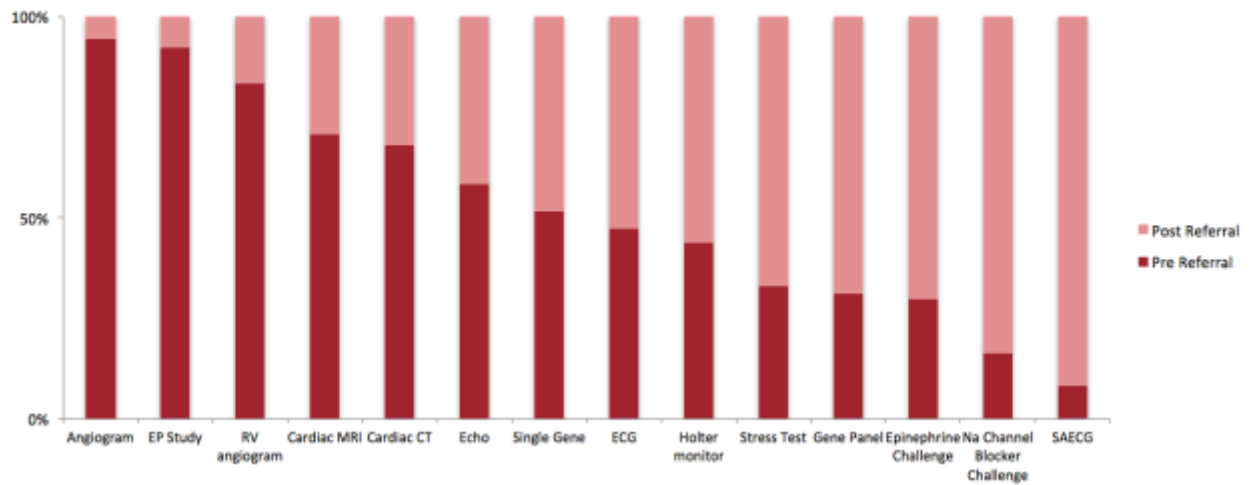
The proportion of evaluations completed before and after referral to the BCIAP varied by test type. The vast majority of angiograms and electrophysiology (EP) studies were completed before referral, while Signal Averaged ECGs and Epinephrine and Procainamide Infusions were typically performed after referral.

A.4   Pre- and Post-Referral Tests Completed
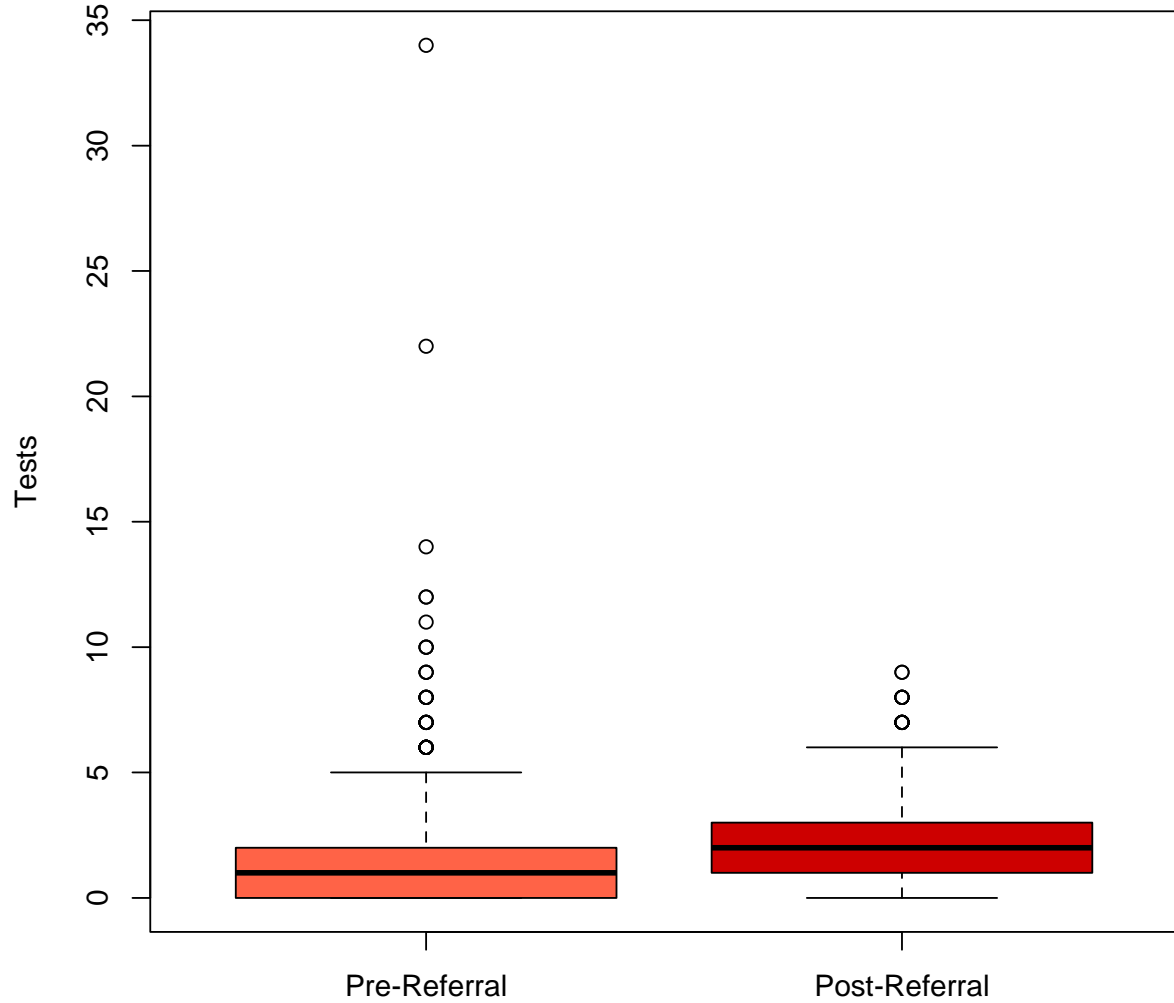
Before referral to BCIAP, patients had a median of 1 (IQR 0-2) tests. After referral, this increased to 2 (IQR 1-3). Patients had significantly more testing after referral to BCIAP (p < 0.001).

A.5   Pre- and Post-Referral Costs
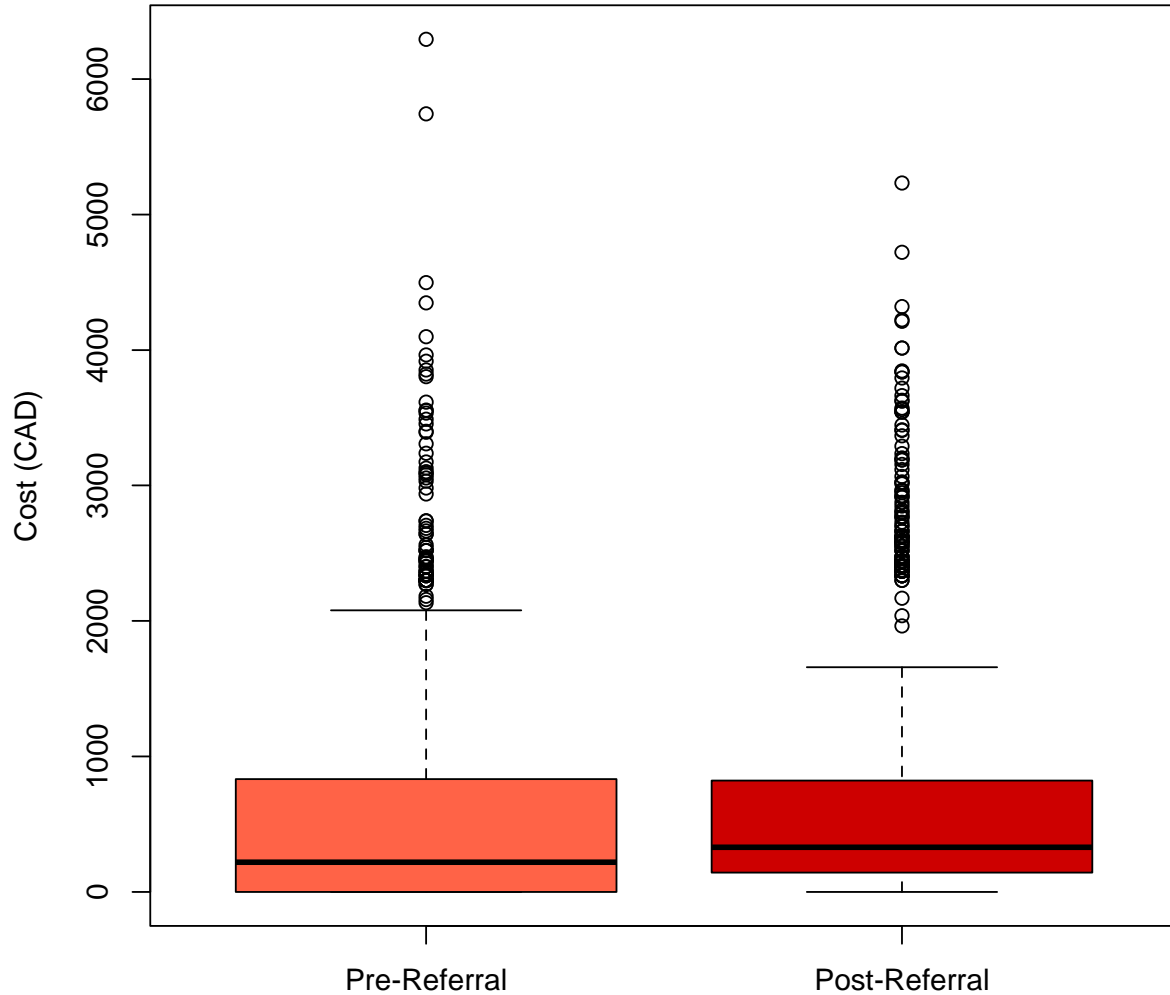
Before referral to BCIAP, testing cost a median $187 per patient (IQR $0-$828). After referral, this increased to $330 (IQR $142-818). The cost per patient was significantly higher after referral to BCIAP (p < 0.001).

A.6   Change in Diagnosis From Referral After BCIAP Evaluation

```
                        Patients with
                         available
                       diagnosis data;
                          n=515
        ┌─────────────────────┴─────────────────────┐
     Primary                                      Family
    Referrals;                                   Members;
     n=249                                        n=266
   ┌─────┴──────────┐              ┌──────────────────┼──────────────────┐
Change in        No change in   Previous testing   Known IHRD in      SUD/SCA in
diagnosis;        diagnosis;       suggsted       family member;   family member;
 n=107             n=142        diagnosis; n=12       n=146             n=108
                ┌────┴────┐
By phenotype;  No change in   Change in            Confirm          IHRD diagnosis;
   n=77       strength; n=51  strength; n=91     diagonsis; n=52         n=26
                           ┌──────┴──────┐
By genotype;          Stronger; n=58   Weaker; n=33  Possible          Possible
   n=3                                            diagnosis; n=22    diagnosis; n=34
                          Change in      Change in
By both; n=27             basis; n=15    basis; n=8   Unaffected;      Unaffected;
                                                        n=72             n=48
                          No change in   No change in
                          basis; n=43    basis; n=25
```

IHRD: Inherited Heart Rhythm Disorder, SUD: Sudden Unexpected Death; SCA: Sudden Cardiac Arrest.

Appendix B Systematic Review Supplemental Materials

B.1   PRISMA Checklist

Section/topic	#	Checklist item	Report page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	39
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	N/A
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	39
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	40
Methods			
Protocol	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	40
Eligbility	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	40
Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	40
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	94
Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	40
Collection	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	40
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	40
Bias in studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	41
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	41
Synthesis	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	41
Bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	41
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	41
Results			
Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exlusions at each stage, ideally with a flow diagram.	53
Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	48

Bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	53
Results	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	52
Synthesis	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	42
Bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	42
Additional	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression).	N/A
Discussion			
Summary	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	44
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	47
Conclusion	26	Provide a general interpretation of the results in the context of other evidence, implications future research.	47
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

B.2   Search Strategy of Medline and Embase

1.	exp anorexia nervosa/ USE mesd
2.	exp anorexia nervosa/ USE emezd
3.	(anorexia or eating disorder*).ti,ab.
4.	or/1-3
5.	exp electrocardiogram/ or exp long QT syndrome USE mesd
6.	exp electrocardiogram/ or exp long QT syndrome USE emezd
7.	qt.mp.
8.	or/5-7
9.	4 and 8
10.	limit 9 to humans
11.	limit 10 to yr="2000-Current"
12.	11 not exp newborn/ not exp infant
13.	12 not (case report* or review* or comment* or editorial* or note* or conference abstract*).pt.
14.	..dedup 13

B.3   Risk of Bias Domains Assessed

Sampling	Is there consecutive or random participant sampling?
Inclusion/Exclusion	Are key inclusion/exclusion criteria clearly stated and defined by valid and reliable measures?
Protocol	Did the study vary from the protocol proposed by the investigators?
Follow-up	Did attrition from any group exceed 20% for short term (<1 year) or 30% for longer term (>1 year) studies? If so, were potential effects on results noted?
Validity	Was the data reviewed manually or automatically?
Reporting	Are important primary outcomes missing from the results?
Measurements	Were valid and reliable measures used consistently across all study participants to assess outcomes, exposures or interventions?
Confounding	Were important confounding and effect modifying variables accounted for in the design and/or analysis?
Detection	Is the study design prospective, retrospective, or mixed?

B.4 Risk of Bias in Individual Studies

Study	Sampling	Inclusion/ Exclusion	Protocol	Follow-up	Validity	Reporting	Measurements	Confounding	Detection
Biadi[128]	Low	Low	Low	N/A	Low	Low	Low	High	Low
Billeci[82]	Low	Low	Low	N/A	High	High	High	Low	Low
DiVasta[167]	Low	Low	Low	High	Low	High	Low	Low	Low
Ertugrul[129]	Low	High	Low	N/A	Low	Unclear	Low	Low	High
Facchini[86]	Low	High	High	N/A	Low	Low	High	Low	Unclear
Franzoni[153]	Unclear	Unclear	Low	Low	Low	High	Low	High	Low
Galetta[89]	Unclear	Low	Low	N/A	Low	Unclear	Low	High	Low
Galetta[4]	Unclear	Low	Low	N/A	Unclear	Unclear	Low	High	Unclear
Krantz[155]	Unclear	High	Low	N/A	Low	Low	Low	High	Low
Krantz[168]	Low	Low	Low	N/A	Low	Low	Low	Low	Low
Mont[56]	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Low
Nahshoni[169]	Low	Low	Low	N/A	Low	Low	Low	Low	Low
Nussinovitch[170]	Unclear	High	Low	N/A	High	Low	Low	High	Low
O'Connor[64]	High	Low	Low	N/A	Low	Low	Low	Low	Low
Olivares[171]	Unclear	High	Low	N/A	Low	High	Low	High	Low
Padfield[75]	Low	Low	Low	N/A	Low	Unclear	Low	High	Unclear
Panagiotopoulos[127]	Low	Low	Low	N/A	Low	Unclear	Low	High	High
Peebles[151]	High	Low	Unclear	N/A	Unclear	High	Low	Low	High
Roche[172]	High	Low	Low	N/A	High	Unclear	Low	Low	Low
Roche[85]	Unclear	High	Low	Low	High	High	Low	Unclear	Low
Takimoto[173]	Unclear	Low	Low	N/A	High	Unclear	High	Low	Low
Ulger[154]	Unclear	Low	Low	Low	Low	High	Low	Low	Low
Vanderdonckt[124]	Low	Low	High	N/A	Low	Low	Low	High	High
Vazquez[174]	Unclear	Low	Low	N/A	Low	Unclear	Low	High	Unclear
Walter[152]	Unclear	Low	Low	N/A	Unclear	Low	Low	Unclear	High
Yahalom[79]	Low	Low	Low	N/A	Unclear	Low	Low	High	High

B.5   Correlates of Corrected QT interval

A. Correlation of BMI and QTc

Study	BMI vs. QTc r value/linear coefficient*	BMI vs. QTc p value
Biadi[128]	NR	NS
DiVasta[167]	-2.5*	NS
Krantz[168]	-0.30	0.20
Nahshoni[169]	NR	NS
Padfield[75]	<0.05	>0.15
Panagiotopoulos[127]	0.28	0.03
Takimoto[173]	NR	NS
Vanderdonckt[124]	0.08	>0.05
Yahalom[79]	-0.522	0.001

B. Correlation of BMI and serum electrolytes.

Study	Electrolyte vs. QTc r value	Electrolyte vs. QTc p value
Franzoni[153]	NR	NS
Galetta[4]	NR	NS
Nahshoni[169]	NR	NS
Vanderdonckt[124]	-0.44	<0.05

B.6   Reporting of Confounding Variables

Study	Illicit drug use	Congenital LQTS	Diabetes mellitus	Medication status	Serum electrolytes
Biadi[128]	NR	Yes	Yes	Yes	Yes
Billeci[82]	NR	NR	NR	NR	Yes
DiVasta[167]	NR	NR	NR	NR	Yes
Ertugrul[129]	NR	NR	NR	NR	NR
Facchini[86]	NR	NR	NR	Yes	Yes
Franzoni[153]	NR	NR	NR	Yes	Yes
Galetta[89]	NR	NR	NR	Yes	Yes
Galetta[4]	NR	NR	NR	Yes	Yes
Krantz[155]	NR	NR	NR	NR	Yes
Krantz[168]	NR	NR	NR	Yes	Yes
Mont[56]	NR	NR	NR	Yes	Yes
Nahshoni[169]	NR	NR	NR	Yes	Yes
Nussinovitch[170]	NR	NR	Yes	Yes	Yes
O'Connor[64]	NR	NR	Yes	NR	Yes
Olivares[171]	NR	NR	NR	NR	NR
Padfield[75]	NR	Yes	NR	Yes	Yes
Panagiotopoulos[127]	NR	NR	NR	NR	Yes
Peebles[151]	NR	NR	NR	NR	Yes
Roche[172]	NR	NR	Yes	NR	NR
Roche[85]	NR	NR	NR	NR	NR
Takimoto[173]	NR	NR	NR	Yes	Yes
Ulger[154]	NR	NR	NR	NR	NR
Vanderdonckt[124]	NR	NR	NR	Yes	Yes
Vazquez[174]	NR	NR	NR	NR	NR
Walter[152]	NR	NR	NR	NR	NR
Yahalom[79]	NR	NR	NR	NR	NR