Cardiac Electrophysiology: Exploring Racial and Gender Outcomes of Treatment of Paroxysmal and Persistent Atrial Fibrillation Using Sotalol and Dofetilide

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CARDIAC ELECTROPHYSIOLOGY: EXPLORING RACIAL AND GENDER OUTCOMES OF TREATMENT OF PAROXYSMAL AND PERSISTENT ATRIAL FIBRILLATION USING SOTALOL AND DOFETILIDE

by

Nicole LaNette Bradford-Love

A dissertation submitted to the Graduate College in partial fulfillment of the requirements for the degree of Doctor of Philosophy Interdisciplinary Health Sciences Western Michigan University December 2020

Doctoral Committee:

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Nicole Franklin, Psy.D.
Adriane MacPhedran, Ph.D.
Purpose

The purpose of this study is to explore the association between gender and racial lines in the conversion and sustainment of normal sinus rhythm (NSR) from paroxysmal atrial fibrillation (PAF) and persistent atrial fibrillation using the anti-arrhythmic drugs (AADs) sotalol and dofetilide.

Methods

A secondary data analysis was performed to assess the relationships of the independent and dependent variables listed above. Using SPSS v. 24 descriptive statistics were obtained and initially evaluated for accuracy with histograms. A cross-tabulation frequency table was produced to determine the number of variables that fell into each dependent category. Following this, the frequencies were checked to ensure that the assumption for chi-square had been met. As the chi-square assumption had not been met with respect to race, this variable was discarded for future data analysis. Fisher’s exact test was used to determine statistical significance of any association between independent and dependent variables. Human Subjects Review Board
approval was obtained at Western Michigan University and the participating institution where the study was performed.
ACKNOWLEDGEMENTS

I would like to thank my committee members Kieran Fogarty, Ph.D., Amos Aduroja, Ph.D., Nicole Franklin, Psy.D., APBB, and Adriane MacPhedran, Ph.D., and my statistician leader, Rob Lyerla, Ph.D. Kieran, your support and patience through this entire process has been nothing short of amazing. I must admit, you definitely got to know me well enough to recognize the ebbs and flows of my academic personality and always seemed to guide me back onto the road of completion from the curb of dissertation despair. Dr. Aduroja, your tenacity and commitment to excellence is contagious and will pass on not only through your students, but everyone who has the beloved opportunity to glean from your greatness. Dr. Franklin, your accomplishments alone cause one to take a deep look at what they can do themselves. There is no limit on how much and how long one would benefit from mentorship. Your commitment to my accomplishment proves that. Our backgrounds and obstacles could not be more similar. We all need that trailblazer at some time in our growth, and at this time, you were mine. Dr. MacPhedran, you hit the ground running with strong and pertinent input, suggestions, critiques, and complements which have all lead to great research.
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being half of anyone else and I am so glad that God didn’t either! My heart beats because of you and now, my heart beats for you.

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To my husband, Lt. Fonte Love, I love you more than all the words in all the books in all the earth. You have been my most steadfast supporter and protector not just during this process but in our lives. It did not escape you the hard work that it took to get through this. I am so grateful for your understanding of the many nights and weekends it seemed that I was married to my books. Your vision of our future was never obscured, and you always knew there were better days to come. You were fearfully and wonderfully made just for me. You are a glisten in the shine of my sun.

This is the day the Lord has made, let us rejoice and be glad in it! Jesus Christ, my Lord and savior, I acknowledge You in everything that I do, for only what we do for You will last. Help me to see everything You see in me because I am Yours. "Like a brush in the hands of an artist, I am Your masterpiece; a thought before life ever started, You took Your time on me.”

Nicole LaNette Bradford-Love

iii
TABLE OF CONTENTS

ACKNOWLEDGEMENTS ........................................................................................................ii
LIST OF TABLES ..................................................................................................................viii
LIST OF FIGURES ...............................................................................................................ix
LIST OF ABBREVIATIONS ..................................................................................................x

CHAPTER

I. INTRODUCTION..............................................................................................................1
   Background ......................................................................................................................6
   Theoretical Framework .................................................................................................11
   Statement of the Problem .............................................................................................12
   Purpose of the Study .....................................................................................................14
   Research Questions .....................................................................................................14
   Significance of the Study ..............................................................................................15
   Definition of Terms .....................................................................................................17
   Assumptions ................................................................................................................18
   Limitations ..................................................................................................................18
   Delimitations ..............................................................................................................19
   Conclusion ..................................................................................................................20
<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>REVIEW OF THE LITERATURE</th>
<th>.................................................................</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>II.</td>
<td>Search Terms</td>
<td>..................................................................................</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Theoretical Framework: Intersectionality</td>
<td>.......................................................................</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Critical Race Theory</td>
<td>..................................................................................</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Growth in Intersectionality</td>
<td>.......................................................................</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Overview of Atrial Fibrillation</td>
<td>........................................................................</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Physical Manifestation of AF</td>
<td>.......................................................................</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Anatomy of the Cardiac Electrical System</td>
<td>..................................................................</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Treatment of AF</td>
<td>..................................................................................</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Conclusion</td>
<td>..................................................................................</td>
<td>49</td>
</tr>
<tr>
<td>III.</td>
<td>RESEARCH METHODOLOGY</td>
<td>..................................................................................</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Research Design</td>
<td>..................................................................................</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Research Questions</td>
<td>..................................................................................</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Hypothesis</td>
<td>..................................................................................</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Study Site</td>
<td>..................................................................................</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Data Collection and Study Population</td>
<td>..................................................</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Independent Variables</td>
<td>..................................................................................</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Dependent Variables</td>
<td>..................................................................................</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Statistical Model</td>
<td>..................................................................................</td>
<td>54</td>
</tr>
</tbody>
</table>
Table of Contents—Continued

CHAPTER

Association in the conversion and sustainment of NSR using sotalol or
dofetilide between whites and non-whites ...........................................73

Contributing Factors to Reduced Enrollment of Non-whites in Clinical Trials 75

Strategies for Improving Enrollment of Non-whites and Females in Clinical
Trials ........................................................................................................77

Limitations ....................................................................................................80

Recommendations for Future Research ....................................................81

Conclusion ....................................................................................................82

References .....................................................................................................84

VII. APPENDICES

A. Western Michigan Human Subjects Institutional Review Board Letter of
Approval .................................................................................................95

B. Mercy Health Human Subjects Institutional Review Board Letter of
Approval .................................................................................................96
LIST OF TABLES

2-1 Classification of Atrial Fibrillation.......................................................................................... 29

4-1 Demographic Data of Catchment Area of the Participating Institution ................................. 58

4-2 Demographic Summary of the Independent Variables............................................................. 59

4-3 Demographic Summary of the Dependent Variables............................................................. 59

4-4 Association Between Gender (IV) and Type of AF (IV) on 1-month post drug load ECG (DV), n=79 ............................................................................................................................. 60

4-5 Association Between Gender (IV) and Type of AF (IV) on 3-month post drug load ECG (DV), n=76 ............................................................................................................................. 61

4-6 Association Between Gender (IV) and Type of AF (IV) on 6-month post drug load ECG (DV), n=76 ............................................................................................................................. 62

4-7 Association Between Gender (IV) and Medication (IV) on 1-month post drug load ECG (DV), n=79 ............................................................................................................................. 63

4-8 Association Between Gender (IV) and Medication (IV) on 3-month post drug load ECG (DV), n=76 ............................................................................................................................. 64

4-9 Association Between Gender (IV) and Medication (IV) on 6-month post drug load ECG (DV), n=75 ............................................................................................................................. 65
LIST OF FIGURES

2-1 ECG interpretation-Medicalbooksvn.wordpress.com, 2018 .................................................. 32

2-2 Cardiac Action Potential........................................................................................................ 36

2-3 ECG PQRS Complex.............................................................................................................. 37

2-4 AAD Effect on Action Potential............................................................................................ 43

2-5 GrepMed, 2019 ....................................................................................................................... 44

5-1 Gorelick et. al, 1998 ............................................................................................................... 78
LIST OF ABBREVIATIONS

AAASPS—African American anti-stroke protection study
AAD—Antiarrhythmic drug
AF—Atrial fibrillation
AFL—Atrial flutter
ACC—American College of Cardiology
AHA—American Heart Association
ARIC—Atherosclerotic risks in communities
AV—atrioventricular
AVN—atrioventricular node
BPM—beats per minute
CAD—coronary artery disease
CBER—Center for Biologics Evaluation and Research
CDC—Centers for Disease Control
CDER—Center for Drug Evaluation and Research
CHF—Congestive Heart Failure
CKD—Chronic kidney disease
CNS—Central nervous system
COPD—Chronic obstructive pulmonary disease
CRT—Critical Race Theory
CVD—Cardiovascular disease
CYP—Cytochrome P450
DOAC—Direct oral anticoagulant
DOE—Dyspnea on exertion
DCCV—Direct current cardioversion
DHHS—Department of Health and Human Services
DM—Diabetes mellitus
ECG—Electrocardiogram
EP—Electrophysiology
FAERS—FDA adverse event reporting system
FDA—Food and Drug Administration
HTN—Hypertension
HLD—Hyperlipidemia
HRS—Heart Rhythm Society
ICS—Inhaled corticosteroids
LA—Left atrium
LABA—Long-acting β2 adrenergic receptor agonist
LIPV—Left inferior pulmonary vein
SVT—Supraventricular tachycardia
TIA—Transient ischemic attack
VF—Ventricular fibrillation
VT—Ventricular tachycardia
INTRODUCTION

Minorities and women are largely underrepresented in clinical trials (Perez-Stable, 2018). A study performed by the Food and Drug Administration (FDA) Office of Women’s Health (2011a) found that African-Americans made up 12% of the United States (U.S.) population but only 5% of clinical trial participants and Hispanics made up 16% of the U.S. population but only 1% of clinical trial participants. Geller, Koch, Pellettieri, and Carnes (2011) analyzed nine medical journals to evaluate the inclusion and analysis of gender in the results of federally funded randomized controlled trials (RCT) in 9 major medical journals in 2009. The clinical trials evaluated were focused in the areas of internal medicine, oncology, cardiology, infectious disease, obstetrics, and gynecology. The journals were selected based on their impact factor in 2003 which is a rating frequency with which articles in the journal are cited in a given year (Geller, Koch, Pellettieri, & Carnes, 2011). The journals included in the study were the New England Journal of Medicine, Journal of the American Medical Association, Annals of Internal Medicine, American Journal of Medicine, Journal of Clinical Oncology, Circulation, Clinical Infectious Disease, Obstetrics and Gynecology, and the American Journal of Obstetrics and Gynecology (Geller et al., 2011). The study found that the average participation of female enrollment in the RCTs that were not gender based was 37%. It also found that 64% of the studies did not report study results by gender (Geller et al., 2011).

Race, ethnicity, and gender play integral roles in inter-individual differences in drug exposure, efficacy, and safety (Ramamoorthy, Pacanowski, Bull & Zang, 2014) and there are
well-established differences in the incidence of disease between males and females and among racial and ethnic groups (Food and Drug Administration Office of Women’s Health [FDA], 2011a). These differences highlight the importance and the need for diversification of gender, race, and ethnicity in clinical trials related to medications and treatments. This is exemplified in well documented health disparities. According to the National Institute of Health (2016), “health disparities are differences that exist among specific population groups in the United States in the attainment of full health potential that can be measured by differences in incidence, prevalence, mortality, burden of disease, and other adverse health conditions.” Minorities and females are disproportionately affected by many disease processes but are underrepresented in the very clinical trials to combat these diseases. For example, according to a comparison done by the FDA in 2005, there were 850,000 new cases of DM between 1998 and 2001. Of those, 37% were black, 24% were white, 36% were Hispanic, 1% were Asian, and 2.1% were classified as other. In clinical trials related to safety, efficacy, exercise, dietary intervention, etc., during approximately the same time period, there was a total of 7,979 participants enrolled. Of those, 85% were white, 10% were black, 4% were Hispanic, 1% were Asian, and 0% were classified as other (FDA, 2011a). Coronary artery disease (CAD) is the leading cause of death in women in the U.S. resulting in 299,578 deaths in 2017 or 1 in every 5 female deaths. Coronary artery disease is also prevalent in men accounting for 321,000 deaths in 2013 or 1 in every 4 male deaths (Centers for Disease Control and Prevention [CDC], 2019b). Despite the similar prevalence and mortality cause by CAD between males and females, females are less likely to be enrolled in clinical trials for cardiovascular disease (CVD) (Ramasubbu, Gurm, & Litaker, 2001). Barriers facing females and non-whites to involvement in clinical trials are manifold. As
it pertains to African-Americans, a lack of awareness about trials, economic factors, communication issues, and mistrust in the medical industry are the most common reasons for lack of participation in clinical trials (Harris, Gorelick, Samuels, & Bempong, 1996). In the case of women, insurance status, inconvenience, availability of transportation, and distance to study site have been cited as reasons for reduced participation (FDA, 2011a).

The FDA has approved many drugs which were deemed safe and effective based on clinical trials that were overwhelmingly representative of white males only to find that months to even years after marketing and use by consumers, some of these drugs were either ineffective or unsafe for non-whites and women (Perez-Stable, 2018; Weyant, 2017). As many of the adverse reactions or variability in a drug's lifecycle are found after the drug has been marketed, reporting of these events becomes paramount to public health and safety (Weyant, 2017). Since 2004, the FDA has provided the FDA’s Adverse Event Reporting System (FAERS) where industry professionals such as health care providers and pharmacists, consumers, and citizens can report adverse events related to drugs (Weyant, 2017). Once an event is reported to the system it is reviewed by clinicians in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) (Weyant, 2017). Concerning reviews may be escalated to investigations by the FDA which may ultimately lead to regulatory action in the form of labeling and use restrictions, post-market prescribing recommendations, individualization of labeling for specific subpopulations, black-box warnings, or the reversal of FDA approval (Ramamoorthy, 2014; Weyant, 2017). A black-box warning is the strongest medication related safety concern that the FDA can issue for a prescription drug (Cheng, Guglielmo, & Maselli, 2010). These warnings are reserved for special
problems that may lead to serious injury or death caused by a medication (Beach, Faich, Bormel, & Sasinowski, 1998). For medications with black-box warnings there is a prominently displayed box surrounding text on the promotional material and package inserts that specifically describes the potential adverse event(s) in an effort to bring attention to the prescribing individual, consumer, and the public (Beach et al., 1998; Weyant, 2017).

According to Wagner et al. (2005), an official list of drugs with black-box warnings does not exist however Weyant (2017) estimates that there are approximately 600 drugs that on the market with black-box warnings. Two pertinent examples with adverse effects on specific subpopulations underrepresented in clinical trials are clopidogrel and salmeterol.

Clopidogrel is an anti-platelet drug often used for patients with atherosclerotic vascular disease and routinely given after a patient has had a myocardial infarction (MI) and percutaneous coronary intervention (PCI) to prevent thromboembolic events associated with enhanced platelet activity (Perez-Stable, 2018; Wagner, 2005). The black-box warning from Bristol-Meyers-Squibb (2019) states:

The effectiveness of this drug depends on conversion to an active metabolite by cytochrome P450 (CYP) system, principally CYP2C19. Consider use of another platelet PY2 inhibitor in patients identified as CYP2C19 poor-metabolizers (p. 2).

A study by Bhopalwala, Hong, Khan, Valentin, and Badawi (2015) revealed that 25-50% of people with East Asian and South Asian backgrounds are CYP2C19 poor-metabolizers which is associated with decreased rates of clopidogrel activation rendering them at increased risk for thrombotic events.
Salmeterol is a long-acting β₂ adrenergic receptor agonist (LABA) used to maintain symptoms of asthma and chronic obstructive pulmonary disease (COPD) (GlaxoSmithKline, 2020). Salmeterol may also be used as a combined medication with inhaled corticosteroids (ICS) (GlaxoSmithKline, 2020). The black-box warning from GlaxoSmithKline (2020) states: Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT DISKUS, as a monotherapy (without inhaled corticosteroids [(ICS)]) increase the risk of asthma-related death. Data from a large placebo-controlled U.S. trial that compared the safety of salmeterol with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 subjects on placebo (p. 2).

The Salmeterol Multi-Center Asthma Research Trial (SMART) was a randomized, double-blind, placebo-controlled observational surveillance study conducted at 6136 U.S. sites between 1996 and 2003 (GlaxoSmithKline, 2020; Nelson, Weiss, Bleecker, Yancy, & Dorinsky, 2006). The purpose of the study was to compare respiratory and asthma-related outcomes in subjects receiving the usual asthma pharmacotherapy with the addition of placebo versus the usual asthma pharmacotherapy with the addition of salmeterol. The study was prematurely terminated due to an interim analysis showing that patients receiving salmeterol were at increased risk of sudden death compared to those who received placebo (GlaxoSmithKline, 2020; Nelson et al., 2006). In comparison to the total population and Caucasian population in the study receiving salmeterol, there were 8 deaths per 10,000 patients in the total population, 6 deaths per 10,000
patients in Caucasian population, and 27 deaths per 10,000 patients in the African-American population (GlaxoSmithKline, 2020, p. 2). These findings further highlight the need for increasing diversity in clinical trials.

This chapter provided an introduction and shall go forward to provide the background of the study and a brief overview of the theoretical framework. It will then describe the statement of the problem, purpose of the study, research questions, and significance of the study. Lastly, it will conclude with definitions of terms, assumptions, limitations, delimitations, and a chapter conclusion.

1.1 Background

The use of a new drug and/or treatment should be based on the results of well designed, unbiased controlled double-blind clinical trials that include people representing the full range of the population most likely to use the drug once it is marketed (King, 2002). According to Knepper and McLeod (2018), the number of countries contributing data to clinical trials for approval of drugs nearly doubled from 32 to 57 between 1997 and 2014, however this increase has not correlated with an increase in the racial diversity of people enrolled in studies. In 1997 according to data from the FDA, 92% of participants in clinical trials were white and in 2014 nearly 86% were white (Knepper & McLeod, 2018). In an effort to determine which populations were used by the FDA to provide safety and efficacy information Knepper and McLeod (2018) reviewed the approvals of new drugs made by the agency over 5 points in time (1997, 2004, 2009, 2012, and 2014) from 1997 to 2014. The focus of the probe was on treatments approved for heart disease, cancer, and disorders of the central nervous system (CNS) as conditions of
these systems are common globally. For each drug approval the race (White, Black, Asian, Other (any person not described as White, Black, or Asian)) of people enrolled and the country in which the people were from were documented. During this time period, 81 drugs were approved based on clinical trials which included nearly 150,000 people from 29 countries including the U.S., Africa, Europe, Asia-Pacific, and Latin America. Despite the growing number of participating countries in clinical trials, over the five points of time, there was no appreciable change in racial enrollment (Knepper & McLeod, 2018). Ethnic minorities continued to be underrepresented while the participating majority remained white. The median percentage of African and African American participants per trial ranged from 1.8% to 3.5%, Asian participants per trial ranged from 0% to 7%, and for those classified as other, participation was 1.4% to 3.4%. At each point in time the vast majority of people enrolled in these clinical trials were white (Knepper & McLeod, 2018).

Among variables such as genetics, age, diet, comorbidities, and concomitant use of other medications, race is an important factor that may affect a patient’s response to new medications (King, 2002). It is imperative to consider race during drug development due to factors that can affect the pharmacokinetics, or the movement of drugs within the body and what the body does to the drug and pharmacodynamics, or the biochemical, physiologic, and molecular effects of drugs on the body that differ among races (Merck, 2019; Ramamoorthy et al., 2014). According to Ramamoorthy et al. (2014), approximately 1/5 of new drugs approved from 2008 to 2014 demonstrated differences in exposure, response, efficacy, and safety in whites when compared to those of other racial and ethnic lines.
One of the most prevalent causes of the differences in exposure, response, efficacy, and safety of drugs across racial and gender lines is related to differences in the body’s metabolism. The liver’s cytochrome CYP450 family of enzymes is designed to metabolize drugs and detoxify the body of foreign chemicals or xenobiotics (Alessandrini, Asfaha, Dogden, Warnich, & Pepper, 2013). There are multiple CYP450 subtypes responsible for the metabolism of specific medications and foreign substances however a complete classification of each subtype would be beyond the scope of this paper. In relating the differences in drug responses relevant to this paper at the interracial level, those subtypes will be discussed.

Although drug metabolism occurs in the intestinal walls, lungs, kidneys, and plasma, the liver is the primary site (Eastabrook, 2003; McDonnell & Dang, 2013). Not all drugs have CYP450 activity however drugs with CYP450 activity may alter the metabolism of other drugs by either inhibiting the enzymatic pathway of CYP450 thus causing increased concentrations of drugs resulting in toxicity. Other drugs may induce the CYP450 pathway thus reducing the concentration of other drugs leading to subtherapeutic drug levels and treatment failures (McDonnell & Dang, 2013). Each person’s ability to metabolize a drug is determined by the pairing of alleles inherited from the mother and father (McDonell & Dang, 2013). Each allele is categorized as a wild-type or variant. People who inherit two wild-type alleles generally have normal rates of metabolism and are referred to as extensive metabolizers. People who inherit two variant alleles will have little to no enzymatic activity and are referred to as poor metabolizers. Lastly, those who inherit one wild-type and one variant allele have decreased enzymatic activity and are referred to as intermediate metabolizers (McDonnell & Dang, 2013). Interracial variability and genetic mutations or polymorphisms are common in the
CYP450 system and may cause unpredictable responses or affect the safety and efficacy of
drugs (McDonnell & Dang, 2013). According to Alessandrini et al. (2013), polymorphisms or
genetic variations account for 30% of interindividual differences seen in a variety of drug
responses however the clinical importance of this system has been extensively studied in the
Caucasian and Oriental population with limited data existing for African populations who
experience a heavy burden of communicable and non-communicable diseases. In a study by
Ramamoorthy et al. (2014) approximately 1/5 of new drugs approved in the previous 6 years
demonstrated differences in exposure and/or response across racial or ethnic groups leading to
population-specific prescribing recommendations. For example, rosuvastatin, a drug used to
treat hyperlipidemia, has a specific recommendation to initiate the drug at a lower dose for
Asians due to clinically relevant differences in pharmacokinetics (Ramamoorthy et al., 2014).
Tacrolimus, a drug used after organ transplantation to reduce the risk of organ rejection is
dependent upon a subtype of the CYP450 enzymatic system, CYP3A5, for metabolism
(2017), found that Tacrolimus has significantly different pharmacokinetics by race with
African Americans having variant alleles. In African Americans Tacrolimus has a 20% to 50%
lower bioavailability, higher drug clearance, and lower concentrations of Tacrolimus in the
blood compared to Caucasians requiring 1.5 to 2 times higher doses to achieve target blood
levels (Sanghavi et al., 2017).

The National Institute of Health (NIH) recognizes that the assumption that all that needs
to be learned about health and health care cannot be learned by studying mostly white male
participants. In response, the NIH required in 1993 that researchers who received funding report
race, ethnicity, and gender of participants in biomedical research (National Institute of health [NIH], (1994).
1.2 Theoretical Framework

The theoretical framework of this study is based upon the work of Crenshaw, the author of the groundbreaking essays, ‘Demarginalizing the Intersection of Race and Sex: A Black Feminist Critique of Antidiscrimination Doctrine, Feminist Theory and Antiracist Politics’ and ‘Mapping the Margins: Intersectionality, Identity Politics, and Violence Against Women of Color’ (Bowleg, 2012). Crenshaw coined the term “intersectionality” to address the marginalization of black women within antidiscrimination law, feminist, and antiracist theory and politics (Crenshaw, 1989). Crenshaw highlights the idea that black women are excluded from feminist theory and antiracist politics because being black and female are predicated on experiences that do not accurately reflect the intersection of race and gender. As intersectionality makes its way into many disciplines including public health, sociology, psychology, criminal justice, and education, its definition and focus have been dynamic. Bowleg, expounded upon the work of Crenshaw with the article ‘The Problem with the Phrase Women and Minorities: Intersectionality-an Important Theoretical Framework for Public Health.’ Bowleg (2012) defines intersectionality as a theoretical framework that seeks to highlight how multiple social identities such as race or ethnicity, gender, sexual orientation or identity, socioeconomic status (SES), geographical location, and physical or mental disability comingle at the microsocial level of individual experience to create systems of privilege and oppression, such as racism, sexism, heterosexism, and classism at the macrosocial structural level and how these interactions perpetuate the chasm of health care disparity. Intersectionality has emerged as a means to address structural forms of inequality in health care.
1.3 Statement of the Problem

Atrial fibrillation (AF) is the most common sustained rhythm disturbance encountered in clinical practice (January, Wann, Alpert, Calkins, Cigarroa, Cleveland… Yancy, 2014). The Centers for Disease Control and Prevention (CDC) (2017a) estimated 2.7 million to 6.1 million people in the U.S. have been diagnosed with AF and that number is expected to increase to 8 million by 2050 (Calkins, Hindricks, Cappato, Kim, Saad, Aguinaga… Yamane, 2017). This source does not delineate the incidence of AF by race or ethnicity. The incidence of AF increases in prevalence with advancing age (January et al., 2014). Approximately 1% of patients with AF are <60 years of age while up to 12% are 75-84 years of age (January, et al., 2014). More than 1/3 of all patients with AF are >80 years of age (January, et al., 2014). For individuals of European descent, the lifetime risk, which quantifies the absolute risk of developing a disease of interest before death, of developing AF after 40 years of age is 26% for men and 23% for women (January et al., 2014). Limited data exists on the incidence and lifetime risk of AF in the African American and other ethnic populations because most studies were performed with predominantly white participants of European origin (Mou, Norby, Chen, O’Neal, Lewis, Loehr… Alonso, 2018). In an effort to narrow this chasm, Mou et al. (2018), performed a large biracial study on participants from the Atherosclerotic Risks in Communities Cohort (ARIC). The ARIC is a biracial prospective cohort study for the investigation of the etiology of cardiac atherosclerosis and its clinical sequelae and variation in cardiovascular risk factors, medical care, and disease based on race, sex, place, and time (The ARIC investigators, 1989). The cohort is composed of 15,792 participants recruited between 1987 to 1989 from Washington County, MD; the northwest suburbs of Minneapolis, MN; Jackson, MS; and Forsyth
County, NC (Mou et al., 2018). Of the participants, 55% were women and 27% were African American reflecting the racial demographic of the underlying population of each community with the exception of Jackson, MS, where only African Americans were sampled. At the time of recruitment, the participants were between the ages of 45 to 64 years old (Mou et al., 2018). Participants in the ARIC were examined three times in approximately 3–year intervals until 1998 with a final examination between 2011 and 2013. Examinations included carotid and popliteal artery ultrasounds; lipid and lipoprotein analyses; coagulation, inhibition, platelet, and fibrinolytic activity evaluations; and surveillance for coronary heart disease which involved the review of hospitalizations and deaths of participants (Mou et al., 2018). Among the ARIC cohort, Mou et al. (2018) included 15,343 participants in the study excluding the following; 48 participants with self-reported race as nonwhite or non-African American; 44 African Americans from MN and MD due to small sample sizes; and 37 participants with AF or atrial flutter (AFL) diagnosed by ECG at the initial visit (Mou et al., 2018). Baseline characteristics of the study participants were 5332 (35%) white males, 5948 (39%) white females, 1539 (10%) African American males, and 2524 (16%) African American females. Atrial fibrillation was identified by electrocardiograms (ECG) from follow-up examinations, hospital discharge records, and death certificates (Mou, et al., 2018). The study identified 2793 new cases of AF; 2272 in whites and 521 in African Americans. Based on their findings the lifetime risk of AF was 36% in white males, 30% in white females, 21% in African American males, and 22% in African American females (Mou et al., 2018).

Atrial fibrillation is a growing problem in the U.S. The consequences of AF can be life changing and life threatening (Calkins, Hindricks et al., 2017; Kim, Johnston, Chu, & Shulman,
2011). Sotalol and dofetilide are two of the most popular and most efficient drugs used to treat AF however the population studied to determine the efficacy and safety of these drugs was overwhelmingly white (90%) and male (70%) (FDA, 2018c), therefore data assessing the efficacy of these medications in non-whites and females are lacking. The outcome of this research may help to confirm or determine the effectiveness of sotalol and dofetilide in non-whites and females. Such results may contribute to literature in the field of cardiac electrophysiology and lead to more diverse clinical trials in the future.

1.4 Purpose of the Study

This study seeks to determine if there is an association between gender and racial factors in the conversion and sustainment of normal sinus rhythm (NSR) from paroxysmal or persistent AF using sotalol or dofetilide at the 1-month, 3-month, and 6-month interval after drug loading. Electrocardiograms performed at approximately the 1-month, 3-month, and 6-month intervals will be used to evaluate each patient’s cardiac rhythm.

1.5 Research Questions

Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol between males and females at the 1-month, 3-month, and 6-month post-loading interval?

Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using dofetilide between males and females at the 1-month, 3-month, and 6-month post-loading interval?
Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol between non-whites and whites at the 1-month, 3-month, and 6-month post-loading interval?

Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using dofetilide between non-whites and whites at the 1-month, 3-month, and 6-month post-loading interval?

1.6 **Significance of the Study**

This study brings to light the underrepresentation of non-whites and females in clinical trials and specifically as it relates to sotalol and dofetilide. The Institute for Safe Medical Practices (2018) considers sotalol and dofetilide high-alert medications. Per the Institute, “high-alert medications are drugs that bear a heightened risk of causing significant harm in patients when they are used in error” (p. 1). As sotalol and dofetilide can cause dangerous life-threatening arrhythmias and renal failure, it is required by the FDA that the patient be placed in a facility for a minimum of three days that can provide continuous electrocardiac monitoring, cardiac resuscitation, calculations of kidney function, and the presence of personnel trained in the management of serious ventricular arrhythmias for the initiation, re-initiation, and dose adjustment of these medications (FDA, 2018c). Both sotalol and dofetilide can cause an increase in the QT interval which is the time from the start of depolarization (contraction of the heart) to the end of repolarization (relaxation of the heart). Increase in this interval longer than .500ms can induce dangerous ventricular arrhythmias, primarily Torsades de Pointes, where the ventricles of the heart beat faster than the atria creating a complex that spirals around the
baseline of an ECG (Thaler, 2015). Torsades de Pointes may terminate on its own or could
deteriorate to ventricular fibrillation (VF) allowing no blood to flow to the rest of the body,
which can lead to cardiac arrest and death (Seymore, 2018).

A randomized, double-blind, placebo-controlled dose response trial evaluated the ability
doefetilide to convert patients with persistent AF or AFL to NSR and to maintain NSR after
conversion. Nine hundred ninety-six patients were enrolled in the study and had a 1-week to 2-
year history of AF or AFL. Patients were randomized to placebo or doses of 125 mcg, 250 mcg,
or 500 mcg of doefetilide twice a day. The study found that at 6 months and 12 months 62% and
58% of patients, respectively, on doefetilide 500 mcg twice a day remained in NSR; 50% and 37% of
patients, respectively, on 250 mcg of doefetilide twice a day remained in NSR; and 37% and 25%
of patients, respectively, on placebo remained in NSR (FDA, 2018c). The patient population in
this study was mostly white (90%) and male (>70%) and made no contribution to outcomes
related to non-whites nor females. The study also does not give the outcomes of patients on 125
mcg of doefetilide. In another U.S. multicenter, randomized, placebo-controlled, double-blind,
dose-response trial of patients with symptomatic primarily paroxysmal AF and AFL, three fixed
dose levels of sotalol 80 mg, 120 mg, and 160 mg twice daily were compared in 253 patients.
The study found the recurrence rate of AF or AFL at 12-months post-conversion was 67% on
placebo, 58% on 80 mg of sotalol, 49% on 120 mg of sotalol, and 42% on 160 mg of sotalol.
The patient population in this study was 64% male (FDA, 2018c). The European and Australian
Multicenter Evaluative Research on Atrial Fibrillation—Dofetilide, or the EMERALD trial,
performed to determine the effectiveness of doefetilide, found that doefetilide was an effective and
well tolerated treatment for AF, however of the 505 study participants, only 22 were female and
there was no documentation of race (EMERALD, 1998). Although these studies do generally address the efficacy of sotalol and dofetilide, the representation of females and non-white participants were minimal. This research will address the efficacy of both drugs in males and females as well as white and non-white patients.

1.7 Definition of Terms

*Cardiac Electrophysiology.* The study of the electrical system of the heart concerning the mechanisms and therapy of cardiac arrhythmias (Fogoros, 2012).

*Electrocardiogram.* A 10-second recording of the innate biologic electrical activity of the heart

*Arrhythmia.* Disturbance of rate, regularity, or conduction of the cardiac impulse (Thaler, 2015).

*Paroxysmal atrial fibrillation.* Atrial fibrillation that terminates spontaneously or with intervention within 7 days of onset (January et al., 2014).

*Persistent atrial fibrillation.* Continuous atrial fibrillation that is sustained for >7 days

*Anti-arrhythmic drugs.* Drugs that change the shape of the action potential thereby altering the shape of the cardiac action potential and the conductivity and refractoriness of cardiac tissue to reduce the likelihood of recurrence of reentrant circuits (Fogoros, 2012).

*Sotalol.* Class III anti-arrhythmic drug with class II properties that block potassium and beta-adrenergic channels causing prolongation of the action potential and refractoriness in slow and fast tissue channels (Fogoros, 2012).

*Dofetilide.* A pure class III anti-arrhythmic drug that blocks the rapid component of the cardiac delayed rectifier potassium current prolonging the cardiac action potential and the effective refractory period (McClellan & Markham, 1999).
1.8 Assumptions

There is no association between males and females and whites and non-whites in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide.

1.9 Limitations

There are many limitations that have been identified in this study. First, the study is performed at one institution which limits generalization of findings. The patient population at this institution is predominantly white and male which could translate into less information regarding the efficacy of sotalol and dofetilide for non-whites and females. Each patient in the study gave documentation of race, however this self-documented variable in some cases could be inaccurate affecting study findings. The study also focuses exclusively on AF and excludes the multitude of other dysrhythmias or dysrhythmias that may co-occur with AF. Some patients in the study have been diagnosed with multiple dysrhythmias which may call for treatment strategies beyond or other than the use of sotalol or dofetilide. These dysrhythmias could cause, exacerbate, or interfere with treatment of AF. Comorbidities like hypertension (HTN), heart failure, CAD, valvular heart disease, obstructive sleep apnea (OSA), and obesity are known to increase the risk of AF as well as possibly reduce the success rate of treatment. This study does not address the link between these comorbidities and the rate of conversion from AF to NSR with the use of sotalol or dofetilide. Behavioral characteristics such as cigarette smoking, illicit drug use disorder, alcohol use or use disorder, and excessive caffeine intake may play a part in the success of treatment of AF. As well, medication compliance may also play a role. Though patients are advised to discontinue these behaviors and fully comply with prescribing
instructions, there is no reasonable way to assure compliance with these recommendations beyond receiving their self-reported documentation. It is noteworthy that evaluation of the patients ECG at the 1-month, 3-month, and 6-month interval may not give the full scope of the patient’s heart rhythm as it relates to time spent in NSR or AF as the ECG only documents a 10-second period of time while the patient is in the office. These patients may well be in AF or other dysrhythmias at other times which would not be captured at the aforementioned intervals. It is possible that patients may convert back to AF after the 6-month interval requiring more aggressive treatment options like AF ablation, atrioventricular-node (AVN) ablation, pacemaker implantation, etc. Progression of treatment has not been documented in this study.

1.10 Delimitations

Delimitations of this study are important and require mentioning in order to clearly highlight necessary boundaries that helped to maintain a focus on the study at hand. First, study subjects are limited to those with paroxysmal or persistent AF although there are many other cardiac dysrhythmias that a patient may have. During the course of the drug-load, some patients may require a direct-current cardioversion (DCCV) in order to promote NSR. Direct-current-cardioversion is a 200 to 360 Joules transthoracic electric shock of the patient’s heart that depolarizes the entire myocardium rendering the heart momentarily refractory to repeat depolarization. This allows the most rapid intrinsic pacemaker which is usually the SA node to resume control of the heart’s rhythm, successfully converting the patient from AF to NSR (Mitchell, 2019b). The rate of conversion to NSR for the patients receiving sotalol or dofetilide who undergo DCCV compared to the patients who do not receive a DCCV during the drug
loading process will not be compared. The method of treatment is limited to sotalol and
dofetilide as these are the most effective drugs for atrial fibrillation and are being used with more
frequency. Evaluation of ECGs at the 1-month, 3-month, and 6-month interval and not
continually monitoring the patients with various forms of devices reduces costs for the patient
that may not be clinically necessary. Lastly, including variables that may affect the outcome of
AF such as heart disease, HTN, OSA, DM, and obesity have already been studied, are well
documented, and would add no new information to the literature.

1.11 Conclusion

It is clear and evident in the literature that some medications, including sotalol and
dofetilide, studied in clinical trials with predominantly white male participants may be
ineffective in females and non-whites. This study will evaluate the effectiveness of sotalol and
dofetilide in males and females and white and non-whites at the 1-month, 3-month, and 6-month
interval after drug loading to determine if they remain in NSR.
CHAPTER II

REVIEW OF THE LITERATURE

This chapter contains seven sections: (1) search terms, (2) theoretical framework: Intersectionality, (3) overview of AF, (4) physical manifestations of AF, (5) basic anatomy of the cardiac electrical system, (5) mechanisms of AF, (6) and (7) treatment of AF.

2.1 Search Terms

Databases used to support this study included PubMed, Scopus, Google Scholar, and ProQuest Health and Medical. Key search terms include: paroxysmal atrial fibrillation, persistent atrial fibrillation, heart rhythm society, left atrium, action potential, treatment of atrial fibrillation, anti-arrhythmic drugs, sotalol, dofetilide, inequities in clinical trials, diversity in clinical trials, and intersectionality.

2.2 Theoretical Framework: Intersectionality

The purpose of this study is to evaluate the association between males and females and whites and non-whites in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide. Non-whites and females are largely underrepresented in clinical trials that determine the effectiveness and safety of drugs; therefore, this study seeks to determine the effectiveness of the aforementioned drugs in these populations. The theoretical framework of this study is based upon the work of Dr. Kimberlé Crenshaw, the author of the groundbreaking essays, 'Demarginalizing the Intersection of Race and Sex: A Black Feminist Critique of Antidiscrimination Doctrine, Feminist Theory and Antiracist Politics' and 'Mapping
the Margins: Intersectionality, Identity Politics, and Violence Against Women of Color" (Bowleg, 2012). In these works, Crenshaw introduced the term intersectionality to address the marginalization of black women within antidiscrimination law, feminist, antiracist theory and politics (Crenshaw, 1989). Crenshaw (1989) states that black women are sometimes excluded from feminist theory and antiracist politics because being black and female are described and represented with inaccurate experiences that do not adequately reflect the intersection of gender and race. Crenshaw (1989) further states that the intersectional experience is “greater than the sum of racism and sexism and that any analysis that does not take intersectionality into account cannot sufficiently address the particular manner in which black women are subordinated” (p. 140). She goes on to expose the ways in which the law has historically defined the confines of race and sex discrimination through the chosen representatives of white women and African-American men leaving out black women and in essence pitting two resistance groups at odds (Carbado, Crenshaw, Mays, & Tomlison, 2013). The concept of intersectionality is not a new one, but dates back to 1851 in a groundbreaking speech by ex-slave Sojourner Truth (National Park Services [NPS], 2017). Sojourner Truth was born into slavery in 1797 in New York. When her master reneged on his promise to free her in 1827 in accordance to the New York Anti-Slave law of 1827, Truth escaped (NPS, 2017). She went on to become one of the most powerful activists for human rights, women’s rights, and the anti-slavery movement. In 1851 at a Women’s Rights Convention in Akron, Ohio, Truth delivered what is now known as the most poignant and powerful women’s rights and abolitionist speeches in American history, ‘Ain’t I a
Woman?’ (NPS, 2017). In her speech, Truth describes the differing treatment of and sentiment afforded to women based on race. She reads:

That man over there says that women need to be helped into carriages, and lifted over ditches, and to have the best place everywhere. Nobody ever helps me into carriages, or over mud-puddles, or gives me any best place! And ain't I a woman? Look at me! Look at my arm! I have ploughed and planted, and gathered into barns, and no man could head me! And ain't I a woman? I could work as much and eat as much as a man - when I could get it - and bear the lash as well! And ain't I a woman? I have borne thirteen children, and seen most all sold off to slavery, and when I cried out with my mother's grief, none but Jesus heard me! And ain't I a woman? (NPS, 2017, p.1).

For other authors, intersectionality has further been described as an analytical paradigm or theoretical framework "for understanding how multiple social identities such as race, gender, sexual orientation, socioeconomic status (SES), and disability intersect at the micro social level of individual experience to reflect interlocking systems of privilege and oppression (i.e. racism, sexism, heterosexism, classism) at the macro social level" (Bowleg, 2012). Davis (2008) defines intersectionality as “the interaction between gender, race, and other categories of difference in individual lives, social practices, institutional arrangements, and cultural ideologies and the outcomes of these interactions in terms of power” (p. 68).
2.3 Critical Race Theory

The important prelude to intersectionality is the Critical Race Theory (CRT). The CRT was developed by legal scholars in an effort to provide a critical analysis of race and racism from a legal standpoint (University of California Los Angeles [UCLA], 2001). It recognizes that racism is and has been interwoven into every system of American society including the law. It explains that the individual racist is of no consequence in order to recognize that the institutional racism dominant in American culture gives rise to the perpetuation of privilege for whites and marginalization of people of color in general (UCLA, 2001). The CRT also denounces the traditions of liberalism and meritocracy based upon the fact that legal discourse defines the law as value-neutral and colorblind. As it pertains to liberalism, the government is posited as a necessary entity to protect individuals from harm by others but may simultaneously pose a threat to people’s liberty. Meritocracy, or the belief that everyone who works hard can attain wealth, power, and privilege is denounced by the fact that each individual is not equally situated with the same opportunities or resources for success, ignoring the systemic inequalities that institutional racism provides (UCLA, 2001). Intersectionality and the CRT point to the multidimensional dynamic of oppression and recognizes that race alone does not provide the answers to disempowerment of the oppressed, but they highlight how a combination of discriminating factors, i.e. gender, sexual orientation, SES, class, geographic location, age, and ableism intertwine and manifest themselves in various settings (UCLA, 2001).
2.4 Growth in Intersectionality

Intersectionality has had marked interdisciplinary and global travels (Carbado et al., 2013). Intersectionality was initially introduced to highlight the fact that black women were not recognized in feminist movements and antidiscrimination law. It has now traveled into public health, biomedicine, sociology, education, history, psychology, and political science (Carbado et al., 2013). For example, Roberts and Jesudason (2013) founders of the social justice organization Generations Ahead, in their essay, ‘Movement Intersectionality: The Case of Race, Gender, Disability, and Genetic Technologies’ describe lessons in applying insights from intersectionality for coalition building and political change. They posit that intersectional analysis can identify and emphasize commonalities and create solidarity between political groups. They employ intersectionality to forge coalitions between previously adverse groups helping them to acknowledge categorical differences and promote commonalities. Their focus is to help differing groups use an intersectional lens to understand each other’s perspective on a given issue revealing both privilege and victimhood, thereby forming a connection around shared experiences of discrimination and marginalization (Carbado et al., 2013; Roberts & Jesudason, 2013). Cho (2013), author of ‘Post-Intersectionality: The Curious Reception of Intersectionality in Legal Scholarship,’ advances the argument that intersectionality is always a work-in-progress and that just because an intersectional analysis has not been done in a particular area of study does not mean that it cannot be done. Cho also attacks the argument that just because the origin of intersectionality centered around race and gender, specifically black women, it does not mean that is immobile and cannot be engaged in other experiences, and that “race and gender
intersectionality merely provided a jumping off point to illustrate the larger point of how identity categories constitute and require political coalitions (Cho, 2013)” (390). Lastly, Artiles (2014), in his article “Untangling the Racialization of Disabilities: An Intersectionality Critique Across Disability Models,” argues that special education scholarship recognizes the importance of the “racialization of disability.” Artiles goes on to explain the benefits and problems associated with various models of examining disability and how intersectionality can be used to see beyond the recognition that disability is racialized and imagine how this racialization is produced (Artiles, 2014; Carbado et al., 2013).

Bowleg (2012) compounded upon the work of Crenshaw in her article ‘The Problem with the Phrase Women and Minorities: Intersectionality-an Important Theoretical Framework for Public Health.’ In her assessment, intersectionality is a theoretical framework that seeks to highlight how multiple social identities such as race or ethnicity, gender, sexual orientation or identity, SES, geographical location, and physical or mental disability comingle at the micro level of individual experience to create systems of privilege and oppression, such as racism, sexism, heterosexism, and classism at the macro social-structural level and how these interactions perpetuate the chasms of health care disparity (Bowleg, 2012). Bowleg (2012) takes issue with the terms “women and minorities” being a staple population in the discourse of public health. The NIH Policy and Guidelines on the Inclusion of Women and Minority Subjects in Clinical Research 2001 amendment provided guidance on including women and minorities as participants in research and reporting on sex, gender, race, and ethnicity. This amendment implies that sex/gender and race/ethnicity are mutually exclusive. There is no recognition that
these two categories can intersect as they do in racial and ethnic women (Bowleg, 2012).

Another confounding factor in this amendment according to Bowleg (2012) is that the word “minority” is multifaceted and may not only include blacks, Hispanics, Asians, etc., but may include lesbian, gay, bisexual, differently able, or mentally disordered people. She identifies that using the terms minority and women erases the existence of people with multiple intersecting discriminatory categorizations like a low-income Asian lesbian with a physical disability. She further takes issue with the U.S. Department of Health and Human Services’ (DHHS) Health and Humans Services Action Plan to Reduce Racial and Ethnic Health Disparities which acknowledges that “characteristics such as race or ethnicity, religion, socioeconomic status (SES), gender, age, mental health, disability, sexual orientation or gender identity, geographic location, or other characteristics historically linked to exclusion or discrimination are known to influence health status (DHHS, 2011a).” In her assessment the use of the term “or” perpetuates the notion that these discriminatory categorizations do not intertwine and further ignores their obvious intersection in many people. According to Bowleg (2012) acknowledgement of the existence of multiple intersecting identities is the first step towards understanding the complexities of health disparities for populations of historically oppressed groups. The other step is the recognition of how these systems of privilege and oppression result in social inequalities and maintain health disparities. According to Bowleg (2012) “the recognition of intersectionality stands to benefit public health in 4 noteworthy ways:
• Providing a unifying language and theoretical framework for public health scholars engaged in investigating intersections of race, ethnicity, gender, sexual orientation, SES, and disability to reduce and eliminate health disparities,

• Prompting public health scholars to conceptualize and analyze disparities and social inequalities in health in the complex and multidimensional ways that mirror the experiences of the population for whom adverse health outcomes are most disproportionate,

• Focusing on macro-level social-structural factors to consider the substantial effects beyond the level of the individual on health, and

• Taking the experiences of historically oppressed or marginalized populations as its vantage point to facilitate and inform the development of well-targeted and cost-effective health promotion, messages, interventions, and policies.”

2.5 Overview of Atrial Fibrillation

Atrial fibrillation is a supraventricular tachycardia (SVT) manifested by chaotic, uncoordinated, and rapid activation of the atria (Calkins, Brugada, Packer, Cappato, Chen, Grijns,…Shemin, 2009). On a surface 12-lead ECG a diagnosis of AF requires a rhythm strip demonstrating irregular R-R intervals and no distinct P waves (Calkins, Hindricks et. al, 2017). The irregularly irregular characteristic of the QRS complex in the absence of P waves is key to identification of AF on a 12-lead ECG (Holler, 2008). The rapid activation of the atria may lead to atrial heart rates of 300 to 500 beats per minute (bpm) and ventricular heart rates that may
exceed the normal ventricular rate of 60-100 bpm (Thaler, 2015). The classification of AF assists providers in determining the type of AF a patient may have as well as short-term and long-term treatment strategies. Table 2-1 documents the classification system used in the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) Guidelines for Management of patients with Atrial Fibrillation (January et al., 2014). Classification of Atrial Fibrillation

Table 2-1
Classification of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal AF</td>
<td>• AF that terminates spontaneously or with intervention within 7 days of onset</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>• Episodes recur with varying frequency</td>
</tr>
<tr>
<td>Long-standing persistent AF</td>
<td>• Continuous AF that is sustained for &gt;7 days</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>• Continuous AF &gt;12 months in duration</td>
</tr>
<tr>
<td></td>
<td>• The term “permanent AF” is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm</td>
</tr>
<tr>
<td></td>
<td>• Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathological attribute of AF</td>
</tr>
<tr>
<td></td>
<td>• Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve</td>
</tr>
</tbody>
</table>

*AF indicates atrial fibrillation

2.6 Physical Manifestation of AF

The chaotic uncoordinated rapid activation of the atria leads to atrial dysynchrony, a condition where the atria do not contract at the same time, which may result in reduction of the filling of the left ventricle with enough blood to sustain adequate systemic perfusion and
hemodynamic stability (Holler, 2008). This may cause patients with AF to experience symptoms such as fatigue, shortness of breath (SOB), dyspnea on exertion (DOE), syncope, pre-syncope, lightheadedness, dizziness, heart pounding, heart racing, and heart palpitations (Holler, 2008). Symptoms may range from mild to severe and some patients may have no symptoms at all. Any or all of these symptoms can negatively impact the patient’s quality of life. (Calkins, Hindricks et al., 2017).

Due to its direct impact on patients and the severity of its complications it is important to diagnose AF. Patients with AF have a 5-fold increase risk of stroke compared to those without AF and an increased risk of sudden death (Calkins, Hindricks et al., 2017). According to the CDC (2017a), 15%-20% of ischemic strokes caused by blood clots or fatty deposits in the vasculature of the brain are attributed to AF. Also, AF related strokes are more severe than strokes that are not related to AF (Calkins, Hindricks et al., 2017; Miller et al., 2005. Beyond ischemic strokes, AF may also cause transient ischemic attacks (TIAs), systemic thromboembolism, and cause or exacerbate heart failure (Wang et al., 2003). Atrial fibrillation has also been linked to a 2-fold increase in dementia, (Calkins, Hindricks et. al, 2017; Jacobs et al., 2015; Wang et al., 2003) and overall mortality (January et al., 2014). Populations with comorbidities such as HTN, DM, thyroid disease, chronic kidney disease (CKD), structural, valvular and ischemic heart disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), anemia, obesity, OSA, tobacco use, and alcohol use or use disorder are at increased risk for the development and sustainment of AF as well as its complications (Amin et
Other risk factors include age, sex, race, family history, and tall stature (Calkins, Hindricks et. al, 2017).

Combined with the complications and sequelae of AF, health care costs are also impacted. In the U.S., AF accounts for more than 450,000 hospitalizations annually and contributes to more than 99,000 deaths (Calkins, Hindricks et al., 2017; Kim et al., 2011). Atrial fibrillation increases health care costs by $8700 per person resulting in a $26 billion increase to national annual health care costs (Calkins, Hindricks et al., 2017; Ganesan, Chew, Hartshorne, Selvanayagam, Aylward, Sanders…& McGavigan, 2016).

2.7 Anatomy of the Cardiac Electrical System

In the normally functioning heart, its electrical impulse originates in the sinoatrial (SA) node located in the high right atrium (Fogoros, 2012). The impulse travels from the SA node across Bachman’s Bundle to provide electrical activity to rest of the right atrium (RA) and the left atrium (LA) (Thaler, 2015). From the SA node, the impulse spreads rapidly to the atrioventricular (AV) node where its conduction is slowed in order to give the atria ample time to completely empty its blood into the ventricles (Fogoros, 2012; Thaler, 2015). The impulse then travels down to the Bundle of His to the ventricles via the His-Purkinje system. The electrical impulse follows the His bundle and travels into the right and left bundle branches. The branches of the Purkinje system delivers electrical impulses via Purkinje fibers to the furthest reaches of the ventricular myocardium which causes a brisk contraction from the ventricles (Fogoros, 2012). Figure 2-1 below represents the movement of the electrical impulse through the heart and their manifestations on the ECG.
2.7.1.1 The Cells of the Heart and the Cardiac Electrical System

The heart is powered by innate biological electricity (Thaler, 2015). The ECG is a basic tool used to record the electrical activity of the heart. It is through abnormalities identified on the recording of the ECG that help in the diagnosis of cardiac dysrhythmias (Thaler, 2015). In their resting state, cardiac or myocardial cells are electrically polarized meaning their inside is negative with respect to their outside (Thaler, 2015). The voltage difference across the cell
membrane is called the transmembrane potential which is -80 to -90 mV (Fogoros, 2012). Electrical polarity is maintained by ion pumps that keep the appropriate distribution of ions, mainly calcium, potassium, sodium, and chloride, in and out of the myocardial cell (Thaler, 2015). In turn, the result is an accumulation of negatively charged ions within the cell (Fogoros, 2012). When myocardial cells are stimulated there is loss of the internal negativity of the cell in a process known as depolarization, which is the cardinal electrical event of the heart. Depolarization is propagated from myocardial cell to myocardial cell in a wave that transcends the entire heart representing a flow of electricity. When that wave reaches a myocardial cell, tiny channels within the cell membrane open allowing for the influx of positively charged ions changing its transmembrane potential, causing the cell to contract in a process called excitation-contraction coupling (Fogoros, 2012; Thaler, 2015). In this process the influx of calcium causes actin and myosin, contractile proteins housed within the myocardial cell, to interact resulting in contraction of the cell (Thaler, 2015). Once depolarization is complete, repolarization, which brings myocardial cells back to their negative resting state, occurs by reversing the flow of ions, primarily calcium, out of the myocardial cell causing it to relax. The waves seen on an ECG are a representation of depolarization and repolarization (Thaler, 2015).

Graphed against time, each depolarization-repolarization cycle of the heart represents what is called an action potential. Each action potential stimulates neighboring cells to depolarize, generating their own action potential until the entire heart has been depolarized with an action potential representing each and every myocardial cell (Fogoros, 2012; Thaler, 2015). The heart spontaneously generates these electrical impulses which are vital for proper and
sustained cardiac function. The pattern and timing of these impulses determine the rate and rhythm of the heart (Fogoros, 2012).

2.7.1.2 The Action Potential

The action potential is divided into 5 phases; phase 0, phase 1, phase 2, phase 3 and phase 4. More simply, it can be thought of as the depolarization phase, repolarization phase, and the resting phase (Fogoros, 2012). Phase 0, or depolarization, occurs when rapid sodium channels in the cell membrane are stimulated to open causing positively charged sodium ions to rush into the cell resulting in a rapid positively directed change in the transmembrane potential (Fogoros, 2012). The stimulation and depolarization of a cardiac cell propagates other nearby cells to depolarize. Notably, the speed of depolarization of one cell determines the speed at which the electrical impulse is propagated across the heart. Therefore, if the speed of depolarization is changed, which would also change the slope of phase 0 of the action potential, the conduction velocity of the cardiac tissue would also be changed (Fogoros, 2012). Once a cell is depolarized, it cannot depolarize again until the ionic influx that occurred is reversed. Therefore, the period between the end of phase 0 to late in phase 3 is called the refractory period of cardiac tissue (Fogoros, 2012). Repolarization roughly correlates with phase 1 through phase 3 of the action potential and represents the width of the action potential. It is understood to return the cardiac action potential to the resting transmembrane potential of -80 to -90 mV (Fogoros, 2012). Phase 1 represents the start of repolarization, inclusive of inactivation of the sodium current, and opening of the potassium channels. Phase 2 is thought to prolong the repolarization phase that begins in phase 1. It is commonly known as the plateau phase mediated by slow calcium
channels which allow positively charged calcium ions to slowly enter the cell, which prolongs the refractory period (Fogoros, 2012). Phase 3 represents final rapid repolarization and activation of calcium channels. Here, final rapid repolarization is mediated by a balance between the slow inward and outward potassium current, inactivation of calcium current, and increased outward current through delayed potassium channels (Fogoros, 2012). The net membrane current becomes outward and the cell repolarizes. Phase 4 is known as the resting phase or the time period between action potentials (Fogoros, 2012). There is largely no net movement of ions across the cell membrane, but for some cells this resting period is not quiet. There is a leakage of ions back and forth across the cell membrane in order to cause a gradual increase in transmembrane potential (Fogoros, 2012). When the transmembrane potential is high enough, appropriate channels open to cause the cell to depolarize which will in turn spread across the myocardium causing other cells to depolarize (Fogoros, 2012). This phase 4 activity is known as automaticity, a mechanism by which the normal heart rhythm is established and maintained (Fogoros, 2012). The illustration below represents the relationship of depolarization, repolarization, the action potential, and ECG manifestations.
Figure 2-2  Cardiac Action Potential
Teachme Physiology, 2020
2.7.1.3 **Left Atrial Anatomy and Electrophysiological Mechanism of AF**

The LA is the most posteriorly located chamber of the heart if viewed anteriorly from the chest (Ho, Cabrera & Sanchez-Quintana, 2012b). The pulmonary veins (PV) enter the posterior portion of the left atrium. These are called the right superior pulmonary vein (RSPV), the right inferior pulmonary vein (RIPV), the left superior pulmonary vein (LSPV), and the left inferior pulmonary vein (LIPV) (Ho, Cabrera & Sanchez-Quintana, 2012b). In a study performed on post-mortem hearts, 74% of the patients had 4 PV orifices, 17% had 5 PV orifices, and 9% had a common PV on the right or the left side (Ho, Cabrera & Sanchez-Quintana, 2004a). Myocardial fibers extend into all the PVs for 1-2 cm (Calkins, Hindricks, et al., 2017). Pulmonary vein focal electrical firing can act as a trigger to start and maintain AF (Gittenberger-deGroot, et al., 2003).
Studies have shown that PV-sleeve myocytes have discrete ion channel and action potential properties that predispose them to arrhythmogenesis (Calkins, Hindricks et al., 2017). Other studies performed in rabbit and canine PVs demonstrate automaticity and triggered activity during manipulations that enhance calcium loading while other studies suggest focal triggers from PVs could have a shorter action potential duration versus the atrium due to larger delayed-rectifier potassium currents and smaller inward calcium currents. Abrupt changes in fiber orientation and sodium channel inactivation by reduced resting potentials may also promote conduction abnormalities (Calkins, Hindricks et al., 2017).

2.7.2 Treatment of AF

Electrophysiology is the study of the electrical functioning of the heart with primary concerns of mechanisms and therapies to treat cardiac dysrhythmias (Fogoros, 2012). The main strategies for treating AF are to prevent thromboembolism or ischemic stroke with anticoagulation, control the heart rate, and to restore the heart rhythm (Fogoros, 2012).

2.7.2.1 Anticoagulation

Atrial fibrillation, whether silent or symptomatic, paroxysmal, or persistent requires protection from thromboembolism and stroke. Anti-thrombotic agents like Warfarin, low molecular weight heparin (LMWH), anti-platelet drugs like aspirin and clopidogrel, and Direct Oral Anti-Coagulants (DOACS) agents like dabigatran, apixaban, and rivoroxiban are being used (January et al., 2014). In order to determine if a patient with AF needs an anti-thrombotic agent, a risk stratification protocol known as the Cha₂DS₂-VASc (CHF, HTN, diabetes mellitus (DM),
prior stroke, TIA or thromboembolism, vascular disease, age >65, age >75 years, female sex) scheme is used. This risk stratification protocol assigns points to patients based on the following criteria; patients with a history of CHF, HTN, DM, valvular heart disease, are 65-74 years of age, or female sex are given 1 point for each positive factor; patients 75 years old or greater or who have had a stroke, TIA, or thromboembolism are given 2 points for each positive factor (January et al., 2014). Nine is the maximum score using this risk stratification scheme. A patient with a score of 0 suggests a low risk for thromboembolism and may not require anticoagulation. A patient with a score of 1 is considered low-moderate risk and should consider anticoagulation. A patient with a score of 2 is considered moderate to high risk and should be treated with anticoagulation (https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk, 2019). The adjusted stroke rate per year increases from 1.3% with a Cha2DS2-VASc score of 1 up to 15.2% with a score of 9 (January et al., 2014).
2.7.2.2 Rate Control

Controlling the heart rate or rate control is another important aspect in the treatment of AF. The ideal adult ventricular heart rate is 60-100 bpm. Rate control may positively impact the patient’s quality of life, reduce morbidity, and decrease the potential for developing tachycardia-induced cardiomyopathy (January et al., 2014). Beta-blockers (i.e. Metoprolol, Esmolol, Carvedilol, and Sotalol) and non-dihydropyridine calcium channel blockers (i.e. Diltiazem and Cardizem) are primarily used for rate control. Digoxin and Amiodarone are also used if there are contraindications or adverse reactions to the patient or if rate control is not achieved with beta-blockers or non-dihydropyridine calcium channel blockers (January et al., 2014). When considering which agent(s) to use for rate control, individual factors must be considered such as the patient’s degree of symptoms, hemodynamic status, presence or absence of CHF, COPD, and potential precipitants of AF (January et al., 2014). For example, patients with COPD should avoid beta-blockers due to possible worsening of breathing conditions and patients with decompensated heart failure should avoid non-dihydropyridine calcium channel blockers due to potential worsening of their cardiac condition. In the acute setting when rapid control of the heart rate is required due to hemodynamic instability intravenous (IV) beta-blockers, IV non-dihydropyridine calcium channel blockers, and IV or oral Amiodarone may be used. Direct-current cardioversion may be used in the acute and non-acute setting if the patient has been on uninterrupted anticoagulation for at least 21 days (January et al., 2014). Anticoagulation is necessary prior to DCCV due to the risk of clot formation in the LA caused by AF which could lead to a stroke.
2.7.2.3 **Rhythm Control**

The next approach to treatment of AF is rhythm control. This approach attempts to keep the patient out of AF and in NSR which may also slow the progression of paroxysmal AF to persistent AF. Persistent AF may lead to electrical and structural remodeling of the heart that may become irreversible with time (Wijffels et al., 1995). According to Wijffels et al. (1995), the duration of paroxysms of AF are important when considering progression to persistent AF. Accordingly, they found that 31% of patients with paroxysms of AF shorter than 2 days transitioned to chronic or persistent AF while 46% of patients with paroxysms of AF 2 days or longer transitioned to chronic or persistent AF. Clinically, the more time a patient spends in AF the more difficult it becomes to keep them in NSR rendering rhythm control methods more difficult and less effective. Therefore, early intervention with rhythm control may be beneficial (Cosio et al., 2008).

Rhythm control is achieved by utilizing antiarrhythmic drugs (AADs) (January et al., 2014). Most AADs are grouped into 4 classes (I-IV) using the Vaughn-Miller system which classifies AADs based on their dominant cellular effect on the cardiac action potential (Mitchell, 2017a). Class I drugs (i.e. Lidocaine, Flecainide, Mexiletine, and Propafenone) are sodium channel blockers that block fast sodium channels slowing conduction in fast-channel tissues. Class II drugs are beta blockers (i.e. Propranolol and Metoprolol) which are anti-sympathetic nervous system agents that affect predominantly slow-channel tissues (SA node and AV node) decreasing the rate of automaticity thereby slowing conduction velocity, and prolonging refractoriness. Class III drugs (i.e. Amiodarone, Sotalol, and Dofetilide) are potassium channel...
blockers which prolong the action potential duration and refractoriness in slow and fast channel tissues. Class IV drugs (i.e. Verapamil and Diltiazem) are non-dihydropyridine calcium channel blockers which depress calcium-dependent action potentials in slow-channel tissues, thus decreasing the rate of automaticity, slowing conduction velocity, and prolonging refractoriness (Mitchell, 2017a). Sotalol has both Vaughan-Williams Class II beta-blocking activity as well as Class III cardiac action potential duration properties. It prolongs the plateau phase of the cardiac action potential in isolated myocardial cells, slows the heart rate, decreases AV nodal conduction, and increases AV-nodal refractoriness (FDA, 2017b). Dofetilide has Vaughn-Williams Class III antiarrhythmic activity by blocking potassium channels (FDA, 2018c). It increases the monophasic action potential due to delayed repolarization, terminates AF, and prevents its re-induction (FDA, 2018c). The net effect of these drugs is to cause interruption in the area of the action potential that is responsible for AF or other dysrhythmias. The illustration below provides a visual tool that shows where these drugs affect the action potential.
Many AADs and combinations of AADs are used to treat AF, however evaluation of each of these is beyond the scope of this paper. Instead, this paper focuses on the use and effectiveness of sotalol and dofetilide.

The Institute for Safe Medical Practices (2018) considers sotalol and dofetilide high-alert medications. Per the Institute, “high-alert medications are drugs that bear a heightened risk of causing significant harm in patients when they are used in error” (p. 1). As sotalol and dofetilide can cause dangerous life-threatening arrhythmias and renal failure, it is required by the FDA that
the patient be placed in a facility for a minimum of three days that can provide continuous electrocardiac monitoring, cardiac resuscitation, calculations of kidney function, and the presence of personnel trained in the management of serious ventricular arrhythmias for the initiation, re-initiation, and dose adjustment of these medications (FDA, 2018c).

Loading patients onto sotalol and dofetilide requires the following process:

1. **Electrocardiographic assessment:** Prior to administration of the first dose of sotalol or dofetilide, the corrected QT (QTc) must be measured with an average of 5-10 heart beats using the Bazett formula (FDA, 2018c). If the QTc is greater than 440 milliseconds (ms) or 500ms in patients with ventricular conduction abnormalities, the medication is contraindicated. If the heart rate is less than 60 beats per minute, the QT interval should be used.

![Figure 2-5 GrepMed, 2019](image-url)
2. **Calculation of the Creatinine Clearance:** The starting dose of sotalol and
dofetilide will be based in part on the patient’s creatinine clearance. The creatinine
clearance must be calculated using the following formula:

\[
\text{Male} = \frac{(140 - \text{age}) \times \text{actual body weight in kilograms (kg)}}{72 \times \text{serum creatinine in milligrams per deciliter (mg/dl)}}
\]

\[
\text{Female} = \frac{(140 - \text{age}) \times \text{actual body weight in kilograms (kg)}}{72 \times \text{serum creatinine in milligrams per deciliter (mg/dl)}}
\]

<table>
<thead>
<tr>
<th>Calculated Creatinine Clearance</th>
<th>Dofetilide Capsule Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 milliliters per minute (ml/min)</td>
<td>500 micrograms (mcg) twice a day</td>
</tr>
<tr>
<td>40-60 ml/min</td>
<td>250 mcg twice a day</td>
</tr>
<tr>
<td>20-&lt;40 ml/min</td>
<td>125 mcg twice a day</td>
</tr>
<tr>
<td>&lt;20 ml/min</td>
<td>dofetilide is contraindicated</td>
</tr>
</tbody>
</table>

*Twice a day is every 12 hours

<table>
<thead>
<tr>
<th>Calculated Creatinine Clearance</th>
<th>Sotalol Capsule Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 milliliters per minute (ml/min)</td>
<td>160 mg twice a day</td>
</tr>
<tr>
<td>40-60 ml/min</td>
<td>120 mg twice a day</td>
</tr>
<tr>
<td>20-&lt;40 ml/min</td>
<td>80 mg twice a day</td>
</tr>
<tr>
<td>&lt;20 ml/min</td>
<td>sotalol is contraindicated</td>
</tr>
</tbody>
</table>

*Twice a day is every 12 hours

3. **Assessment of electrolytes:** Serum potassium should be at least 4 mEQ and serum
magnesium should be at least 2 mg/dl. If the patient’s serum potassium is below 4
mEq they must receive 40 mEq daily of potassium while on dofetilide. If the patient’s magnesium is below 2 mg/dl they must receive 2 mg of magnesium IV push and the next day start on oral magnesium of 400 mg twice a day.

4. **Select starting dose of sotalol or dofetilide:** The starting dose of sotalol and dofetilide should be selected based on the calculation of the QT or QTc and the creatinine clearance.

5. **Begin continuous cardiac monitoring:** The patient should be placed on continued cardiac monitoring prior to being given the first dose of sotalol or dofetilide.

6. **First dose electrocardiographic assessment:** Two to three hours after administration of each dose of sotalol or dofetilide the QT or QTc must be reassessed. If the QT or QTc has increased by more than 15% compared to the baseline established in Step 1, is greater than ½ of the R-R interval, or greater than 500ms or 550ms in patients with ventricular conduction abnormalities, the following adjustment in dosing must be made:

<table>
<thead>
<tr>
<th>Starting dose of dofetilide</th>
<th>Adjusted dose of dofetilide</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mcg twice a day</td>
<td>250 mcg twice a day</td>
</tr>
<tr>
<td>250 mcg twice a day</td>
<td>125 mcg twice a day</td>
</tr>
<tr>
<td>125 mcg twice a day</td>
<td>125 mcg once a day</td>
</tr>
</tbody>
</table>

*Twice a day is every 12 hours*
Starting dose of sotalol | Adjusted dose of sotalol
---|---
160 mg twice a day | 120 mg twice a day
120 mg twice a day | 80 mg twice a day
80 mg twice a day | 80 mg once a day

*Twice a day is every 12 hours

7. **Subsequent creatinine clearance and electrolyte assessment:** The patient’s creatinine clearance, potassium, and magnesium must be assessed each day during the drug loading process. Based on the patient’s subsequent creatinine clearance calculations, the following adjustments to the sotalol and dofetilide dosage should be made;

| Reduction in creatinine clearance | Starting dofetilide dose | Adjusted dofetilide dose
---|---|---
>60 milliliters per minute (ml/min) | 500 micrograms (mcg) twice a day | Continue current dose
40-60 ml/min | 250 mcg twice a day | 125 mcg twice a day
20-<40 ml/min | 125 mcg twice a day | Discontinue dofetilide

*Twice a day is every 12 hours

| Reduction in creatinine clearance | Starting sotalol dose | Adjusted sotalol dose
---|---|---
>60 milliliters per minute (ml/min) | 160 mg twice a day | Continue current dose
40-60 ml/min | 120 mg twice a day | 80 mg twice a day
20-<40 ml/min | 80 mg twice a day | 80 mg once a day
<20 ml/min | sotalol is contraindicated | sotalol is contraindicated

*Twice a day is every 12 hours
8. **Subsequent electrocardiographic assessment:** Two to three hours after each subsequent dose of sotalol or dofetilide the QT or QTc must be reassessed for at least 5 doses. Patients must be continuously monitored by ECG for a minimum of 12 hours after pharmacological conversion to NSR has occurred (FDA, 2018c).

Since sotalol and dofetilide can cause an increase in the QT interval which could lead to dangerous ventricular dysrhythmias, patients must be removed from any other drugs that may increase the QT interval (i.e. Methadone, Amiodarone, and Zithromax). Patients should discontinue these drugs for the specified amount of time (based on the drugs half-life) for the drug to metabolize completely from the blood stream. As long as the patient remains on sotalol or dofetilide, no QT prolonging drugs may be used.

2.7.2.4 **Direct-Current-Cardioversion (DCCV)**

Direct-current cardioversion is external electrical energy that is passed through the patient’s heart via the thorax using between 200-360 Joules delivered by two paddles (Sucu, Davutoglu, & Ozer, 2009). This is an effective treatment option for patients with AF and other types of dysrhythmias to restore them to NSR. The patient is first sedated then has electrodes attached to the chest and back. Direct-current cardioversion is then delivered as a shock. The patient’s heart rhythm is evaluated subsequent to each shock. This procedure can be repeated multiple times until the patient’s heart rhythm is back in NSR. If sustained NSR is not established after an appropriately delivered number of DCCV shocks, the procedure is deemed
unsuccessful and unable to restore NSR. Other treatment options should then be considered (Mayo Clinic, 2019).

2.7.2.5 Radio Frequency Ablation (RFA) with Pulmonary Vein Isolation (PVI)

Radiofrequency energy is a heat source used to create scarring in the tissue (HRS, 2019). In radiofrequency ablation (RFA), catheters are advanced from the right femoral vein in the groin and into the RA via the inferior vena cava. The septum of the heart is then punctured to access the LA. Radiofrequency energy is then used to create a scar around each PV by creating point-by-point circumferential lesions around each vein isolating them from the body of the LA (HRS, 2019). This technique attempts to control the triggers of AF by blocking the electrical signals generated by the PVs thereby reducing or eliminating the frequency of AF (Gittenberger-deGroot, et al., 2003).

2.8 Conclusion

In conclusion, the exclusion of females and non-whites from clinical trials and the impact this has on the safety and efficacy of medications in these populations has been displayed. This chapter has described an overview of cardiac anatomy, electrophysiology, atrial fibrillation, and treatment mechanisms. It is noteworthy that there are many types of cardiac rhythm disturbances and other medical and procedural treatment options available such as atrioventricular node (AVN) ablation and the insertion of pacemakers, that are beyond the scope of this paper. Chapter III describes the methods for this research study.
CHAPTER III

RESEARCH METHODOLOGY

The focus of this study is to explore the association between males and females and whites and non-whites in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide.

This chapter begins with a description of the study design, research setting, and study population which will include a complete demographic table. This will follow with a description and explanation of the independent variables, dependent variables, a statistical model, and conclude with the statistical analysis of the data.

3.1 Research Design

This is a secondary data analysis performed on the existing data of all patients diagnosed with paroxysmal or persistent AF who were treated with sotalol or dofetilide between January 1, 2018 and December 19, 2019 to determine the relationship of the independent and dependent variables listed below. The patients evaluated in this study represents all of the available patients with paroxysmal or persistent atrial fibrillation who were treated with sotalol or dofetilide during this time period.
3.2 Research Questions

Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol between males and females at the 1-month, 3-month, and 6-month post-loading interval?

Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using dofetilide between males and females at the 1-month, 3-month, and 6-month post-loading interval?

Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol between whites and non-whites at the 1-month, 3-month, and 6-month post-loading interval?

Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using dofetilide between whites and non-whites at the 1-month, 3-month, and 6-month post-loading interval?

3.3 Hypothesis

There is no association between males and females or whites and non-whites in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide.

3.4 Study Site

The study was performed at a 409 licensed-bed primary, acute, and specialty care system in the Midwest. It is a teaching hospital and one of largest health systems in West Michigan with 375 physicians, 3,500 colleagues, 17,000 inpatient discharges, and nearly 145,000 emergency
and/or urgent care visits annually. It offers a number of specialty care services, including cardiothoracic surgery, cardiac electrophysiology, neurosurgery, orthopedics, bariatric surgery and spine services (Mercy Health, 2019). The catchment area of the site is urban and rural with a population of approximately 558,000. The served population is 84.6% white, 3.6% black, 8% Hispanic, 1% native American Indian/Alaskan, and 1% Asian (Community Health Needs Assessment, 2019).

3.5 Data Collection and Study Population

Patient’s records were accessed via the participating institution’s electronic health record. All patient records accessed were loaded onto sotalol or dofetilide for paroxysmal or persistent atrial fibrillation between January 1, 2018 to December 19, 2019. Obtained from the patient’s record were the type of atrial fibrillation diagnosed, the medication sotalol or dofetilide, ECG results at their 1-month, 3-month, and 6-month follow-up appointments, race, and gender. Identifiable patient information such as names, social security numbers, dates of birth and addresses were not used.

3.6 Independent Variables

**Paroxysmal AF.** Paroxysmal AF terminates spontaneously or with intervention within 7 days of onset with episodes that may recur with varying frequency (January et al., 2014).

**Persistent AF.** Persistent AF is continuous and sustained for more than 7 days (January et al., 2014).
Gender and Race. Women of European descent have a lifetime risk of developing AF after the age of 40-years old of 23% (January et al., 2014). Though the risk of developing AF in women is significant, studies have borne out that the population in clinical trials for the development of medication, including sotalol and dofetilide, are overwhelmingly white and male (Perez-Stable, 2018).

Dofetilide. Dofetilide has been found to be effective in converting and maintaining patients with AF in NSR (FDA, 2018c).

Sotalol. Sotalol has been found to be effective in converting and maintaining patients with AF in NSR though it does not appear to be as effective as dofetilide (FDA, 2018c).

3.7 Dependent Variables

ECG Results at 1-month follow up. The patient’s ECG is evaluated 1-month post sotalol or dofetilide load to ensure the patient is in NSR and that the QT or QTc has not prolonged. Prolongation of the QT or QTc may call for dose adjustment or discontinuation. Early in the treatment process, it is important to keep the patient in NSR as much as possible while the heart remodels and the left atria shrinks which reduces the chances of recurrence of AF. If a patient is found to be in AF 1 month following drug-loading, they will be offered DCCV as a means to reestablish NSR.

ECG Results at 3 and 6-month follow-up. The patient’s ECG is evaluated 3-months post sotalol or dofetilide load again to ensure maintenance of NSR and that the QT or QTc has not prolonged. If the patient’s QT or QTc has prolonged dose adjustment or discontinuation may be necessary. If the patient is found to be in AF at 3-months post drug-loading DCCV may be
offered along with continuation of the drug in an attempt to obtain long-term effectiveness. If the patient does not desire to have a DCCV performed, then advancement of treatment options may be considered such as AF ablation with PVI or AV-node ablation, and the insertion of a pacemaker. If the patient’s QT or QTc has prolonged at the 6-month follow up it would be determined that the medication may not be safe for the patient and advancement of treatment strategies may be considered.

### 3.8 Statistical Model

![Statistical Model Diagram]

### 3.9 Data Analysis

A secondary data analysis was performed to assess the relationships of the independent and dependent variables listed above. Using SPSS v. 24 descriptive statistics were obtained and
initially evaluated for accuracy with histograms. A cross-tabulation frequency table was produced to determine the number of variables that fell into each category. Following this, the frequencies were checked to ensure that the assumption for chi-square had been met. As the chi-square assumption had not been met with respect to race, this variable was discarded for future data analysis. Cross-tabulation was continued with the independent variables type of atrial fibrillation and medication. Chi-square analysis to determine statistical significance was violated due to cells having expected counts less than 5, therefore Fisher’s Exact was analyzed in order to determine statistical significance. Fisher’s Exact revealed insignificant p-values for each analysis requiring acceptance of the null hypothesis that there is no association between the independent and dependent variables. Logistic regression was not performed as cross-tabulation and Fisher’s exact revealed that the variables in question were not dependent. Human Subjects Review Board approval was obtained at Western Michigan University and the participating study site.

3.10 Conclusion

This chapter describes the research design, research questions, hypothesis, data collection, and analysis for this study. Chapter IV will describe the results of the study.
CHAPTER IV

RESEARCH FINDINGS

4.1 Results

Based on the methodology described in the previous chapter, this chapter presents, the data analysis, and results of the study. A review of the purpose of the study and research questions will be presented first. Next, the descriptive findings of the study subjects are presented along with data analysis to answer research questions. The chapter concludes with racial and gender comparison results detailing the comparison of sotalol and dofetilide.

4.2 Purpose of the Study and Research Questions

The purpose of this study was to evaluate the association between males and females, and whites and non-whites in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide.

This chapter addresses the overall hypothesis and the four defining research questions. The hypothesis is as follows: There is no association between males and females or whites and non-whites in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide. The four defining research questions developed to explore the hypothesis include:
1. Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol between males and females at the 1-month, 3-month, and 6-month post-loading interval?

2. Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using dofetilide between males and females at the 1-month, 3-month, and 6-month post-loading interval?

3. Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol between whites and non-whites at the 1-month, 3-month, and 6-month post-loading interval?

4. Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using dofetilide between whites and non-whites at the 1-month, 3-month, and 6-month post-loading interval?

4.3 Descriptive Findings of Study Sample

This section of Chapter IV describes the data collection and demographics of the catchment area and study participants. Data analysis of the independent and dependent variables are described and displayed in table format. Finally, statistical analysis is described and displayed in table format which leads to the next section of Chapter IV to answer the research questions.

The subjects of the study were obtained from the electrophysiology program of the participating institution from 1/1/2018 to 12/19/2019. The researcher obtained data from the
electronic health record of patients diagnosed with paroxysmal and persistent AF who were loaded onto sotalol or dofetilide. The sample for the study included 84 subjects.

4.3.1 Demographics

The catchment area of the participating institution is urban and rural and consists of approximately 558,000 people. Of the population served by this institution, 84.6% are white, 3.6% are black, 8% are Hispanic, 1% are Native American Indian/Alaskan, and 1% are Asian (see Table 4-1).

Table 4-1
Demographic Data of Catchment Area of the Participating Institution

<table>
<thead>
<tr>
<th>Racial/Ethnic Category</th>
<th>Total n=558,000</th>
<th>Percentage of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>472,068</td>
<td>84.6%</td>
</tr>
<tr>
<td>Black</td>
<td>200,888</td>
<td>36.0%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>44,640</td>
<td>8.0%</td>
</tr>
<tr>
<td>Native American</td>
<td>5,580</td>
<td>1.0%</td>
</tr>
<tr>
<td>Asian</td>
<td>5,580</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Data were collected by review of patient’s chart via the electronic health record of the participating institution. Eighty-four subjects met the inclusion criteria for study which were a diagnosis of persistent or paroxysmal AF, loaded on to sotalol or dofetilide between 1/1/2018 to 12/19/2019, taking sotalol or dofetilide during the study period, and having had at least one post-drug load ECG. Of the 84 subjects included in the study, 59 were male, 29 were female, 80 were white, 4 were non-white, 62 had a diagnosis of persistent AF, 22 had a diagnosis of paroxysmal AF, 73 were loaded onto dofetilide, and 11 were loaded on to sotalol (see Table 4-2). Race was
excluded from further study as there were not enough non-white study subjects to satisfy statistical analysis. Table 4-3 displays the summary of dependent variables.

Table 4-2
Demographic Summary of the Independent Variables

<table>
<thead>
<tr>
<th></th>
<th>Total n=84</th>
<th>Percentage of Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td>65.5</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>34.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>80</td>
<td>95.2</td>
</tr>
<tr>
<td>Non-white</td>
<td>4</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Table 4-3
Demographic Summary of the Dependent Variables

<table>
<thead>
<tr>
<th>Post-drug load ECG</th>
<th>Total</th>
<th>NSR</th>
<th>AF/other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-month</td>
<td>79</td>
<td>66</td>
<td>13</td>
</tr>
<tr>
<td>3-month</td>
<td>76</td>
<td>65</td>
<td>11</td>
</tr>
<tr>
<td>6-month</td>
<td>75</td>
<td>61</td>
<td>14</td>
</tr>
</tbody>
</table>

Notes. ECG=electrocardiogram; NSR=normal sinus rhythm; AF=atrial fibrillation

4.4 Data Analysis

Pearson’s chi-square and Fisher’s Exact tests were used to explore associations between dichotomous categorical independent variables (type of AF, medication, and gender) and dichotomous categorical dependent variables (1-month ECG, 3-month ECG, and 6-month ECG readings). The null hypothesis is as follows: There is no association between males and females or whites and non-whites in the conversion and sustainment of NSR from paroxysmal or
persistent AF using sotalol or dofetilide. Table 4-4 describes the association between gender and the type of AF and the outcome of the 1-month post-drug load ECG.

Table 4-4

<table>
<thead>
<tr>
<th>Gender</th>
<th>Type of AF</th>
<th>NSR (%)</th>
<th>AF/other (%)</th>
<th>Total (%)</th>
<th>Sig*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>paroxysmal</td>
<td>5 (100)</td>
<td>0 (0.0)</td>
<td>5 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>persistent</td>
<td>16 (72.7)</td>
<td>6 (27.3)</td>
<td>22 (100)</td>
<td>0.555</td>
</tr>
<tr>
<td>Male</td>
<td>paroxysmal</td>
<td>15 (93.8)</td>
<td>1 (6.3)</td>
<td>22 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>persistent</td>
<td>30 (83.3)</td>
<td>6 (16.7)</td>
<td>36 (100)</td>
<td>0.415</td>
</tr>
<tr>
<td>Total</td>
<td>paroxysmal</td>
<td>20 (95.2)</td>
<td>1 (4.8)</td>
<td>21 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>persistent</td>
<td>46 (79.3)</td>
<td>12 (20.7)</td>
<td>58 (100)</td>
<td>0.167</td>
</tr>
</tbody>
</table>

Note. AF=atrial fibrillation. NSR=normal sinus rhythm. Sig*=Fishers Exact

Analysis found that 100% of females with paroxysmal AF converted to NSR compared to 93.8% of males at the 1-month post-drug load period. In patients with persistent AF, 72.7% of females converted to NSR at the 1-month post-drug load period compared to 83.3% of males. Primary outcome results indicate a non-significant association between males and females and the type of AF in the conversion and sustainment of NSR using sotalol or dofetilide at the 1-month post-drug load period $p=.167$. See Table 4-4.

Table 4-5 describes the association between gender and the type of AF and the outcome of the 3-month post-drug load ECG. Analysis found that 100% of females with paroxysmal AF converted to NSR compared to 100% of males at the 3-month post-drug load period. In patients with persistent AF, 81.8% of females converted to NSR at the 3-month post-drug load period.
compared to 79.4% of males. Primary outcome results indicate a non-significant association between males and females and the type of AF in the conversion and sustainment of NSR from paroxysmal AF or persistent AF using sotalol or dofetilide at the 3-month post-drug load period $p=.057$. See Table 4-5.

Table 4-5  
*Association Between Gender and Type of AF on 3-month post drug load ECG, n=76*

<table>
<thead>
<tr>
<th>Gender</th>
<th>Type of AF</th>
<th>NSR (%)</th>
<th>AF/other (%)</th>
<th>Total (%)</th>
<th>Sig*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>paroxysmal</td>
<td>5 (100)</td>
<td>0 (0.0)</td>
<td>5 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>persistent</td>
<td>18 (81.8)</td>
<td>4 (18.2)</td>
<td>22 (100)</td>
<td>0.561</td>
</tr>
<tr>
<td>Male</td>
<td>paroxysmal</td>
<td>15 (100)</td>
<td>0 (0.0)</td>
<td>15 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>persistent</td>
<td>27 (79.4)</td>
<td>7 (20.6)</td>
<td>34 (100)</td>
<td>0.084</td>
</tr>
<tr>
<td>Total</td>
<td>paroxysmal</td>
<td>20 (100)</td>
<td>0 (0.0)</td>
<td>20 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>persistent</td>
<td>45 (80.4)</td>
<td>11 (19.6)</td>
<td>56 (100)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Note. AF=atrial fibrillation. NSR=normal sinus rhythm. Sig*=Fishers Exact

Table 4-6 describes the association between gender and the type of AF and the outcome of the 6-month post-drug load ECG. Analysis found that 100% of females with paroxysmal AF converted to NSR compared to 71.4% of males at the 6-month post-drug load period. In patients with persistent AF, 86.4% of females converted to NSR at the 6-month post-drug load period compared to 80.0% of males. Primary outcome results indicate a non-significant association between males and females and the type of AF in the conversion and sustainment of NSR from paroxysmal AF or persistent AF using sotalol or dofetilide at the 6-month post-drug load period $p=.446$. See Table 4-6.
Table 4-6

Association Between Gender and Type of AF on 6-month post drug load ECG, n=76

<table>
<thead>
<tr>
<th>Gender</th>
<th>Type of AF</th>
<th>NSR (%)</th>
<th>AF/other (%)</th>
<th>Total (%)</th>
<th>Sig*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>paroxysmal</td>
<td>4 (100)</td>
<td>0 (0.0)</td>
<td>4 (100)</td>
<td>0.592</td>
</tr>
<tr>
<td></td>
<td>persistent</td>
<td>19 (86.4)</td>
<td>3 (13.6)</td>
<td>22 (100)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>paroxysmal</td>
<td>10 (71.4)</td>
<td>4 (28.6)</td>
<td>14 (100)</td>
<td>0.084</td>
</tr>
<tr>
<td></td>
<td>persistent</td>
<td>28 (80)</td>
<td>7 (20.0)</td>
<td>35 (100)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>paroxysmal</td>
<td>14 (77.8)</td>
<td>4 (22.2)</td>
<td>16 (100)</td>
<td>0.446</td>
</tr>
<tr>
<td></td>
<td>persistent</td>
<td>47 (85.2)</td>
<td>10 (17.5)</td>
<td>57 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Note. AF=atrial fibrillation. NSR=normal sinus rhythm. Sig*=Fishers Exact

Table 4-7 describes the association between gender and the use of dofetilide or sotalol and the outcome of the 1-month post-drug load ECG. Analysis found that 85.5% of females on dofetilide converted to NSR compared to 89.4% of males at the 1-month post-drug load period. In patients on sotalol, 50.0% of females converted to NSR at the 1-month post-drug load period compared to 80.0% of males. Primary outcome results indicate a statistically significant association between males and females and the use of sotalol or dofetilide in the conversion and sustainment of NSR from paroxysmal AF or persistent AF at the 1-month post-drug load period p=.015. See Table 4-7. In evaluation of this statistically significant result future research on a larger and more gender diverse sample size is needed to clearly understand this particular outcome.
Table 4-7
Association Between Gender and Medication on 1-month post drug load ECG (DV), n=79

<table>
<thead>
<tr>
<th>Gender</th>
<th>Medication</th>
<th>NSR (%)</th>
<th>AF/other (%)</th>
<th>Total (%)</th>
<th>Sig*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>dofetilide</td>
<td>18 (85.5)</td>
<td>3 (14.3)</td>
<td>21 (100)</td>
<td>0.101</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
<td>6 (100)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>dofetilide</td>
<td>42 (89.4)</td>
<td>5 (6.3)</td>
<td>47 (100)</td>
<td>0.129</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>3 (60.0)</td>
<td>2 (40.0)</td>
<td>5 (100)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>dofetilide</td>
<td>60 (88.2)</td>
<td>8 (11.8)</td>
<td>68 (100)</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>6 (54.4)</td>
<td>5 (45.5)</td>
<td>11 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Note. AF=atrial fibrillation. NSR=normal sinus rhythm. Sig*=Fishers Exact

Table 4-8 describes the association between gender and the use of dofetilide or sotalol and the outcome of the 3-month post-drug load ECG. Analysis found that 85.7% of females on dofetilide converted to NSR compared to 86.7% of males at the 3-month post-drug load period. In patients on sotalol, 83.3% of females converted to NSR at the 3-month post-drug load period compared to 75.0% of males. Primary outcome results indicate a non-significant association between males and females and the use of sotalol or dofetilide in the conversion and sustainment of NSR from paroxysmal AF or persistent AF at the at the 3-month post-drug load period $p=.444$. See Table 4-8.
Table 4-8  
**Association Between Gender and Medication on 3-month post drug load ECG, n=76**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Medication</th>
<th>NSR (%)</th>
<th>AF/other (%)</th>
<th>Total (%)</th>
<th>Sig*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>dofetilide</td>
<td>18 (85.7)</td>
<td>3 (14.3)</td>
<td>21 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
<td>6 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>dofetilide</td>
<td>39 (86.7)</td>
<td>6 (13.3)</td>
<td>45 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>3 (75.0)</td>
<td>1 (25.0)</td>
<td>4 (100)</td>
<td>0.472</td>
</tr>
<tr>
<td>Total</td>
<td>dofetilide</td>
<td>57 (86.4)</td>
<td>9 (13.6)</td>
<td>66 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>8 (80)</td>
<td>2 (20)</td>
<td>10 (100)</td>
<td>0.444</td>
</tr>
</tbody>
</table>

Note. AF=atrial fibrillation. NSR=normal sinus rhythm. Sig*=Fishers Exact

Table 4-9 describes the association between gender and the use of dofetilide or sotalol and the outcome of the 6-month post-drug load ECG. Analysis found that 90% of females on dofetilide converted to NSR compared to 77.8% of males at the 6-month post-drug load period. In patients on sotalol, 83.3% of females converted to NSR at the 6-month post-drug load period compared to 75.0% of males. Primary outcome results indicate a non-significant association between males and females and the use of sotalol or dofetilide in the conversion and sustainment of NSR from paroxysmal AF or persistent AF at the 6-month post-drug load period $p=.598$. See Table 4-9.
Table 4-9  
*Association Between Gender and Medication on 6-month post drug load ECG, n=75*

<table>
<thead>
<tr>
<th>Gender</th>
<th>Medication</th>
<th>NSR (%)</th>
<th>AF/other (%)</th>
<th>Total (%)</th>
<th>Sig*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>dofetilide</td>
<td>18 (90.0)</td>
<td>2 (10.0)</td>
<td>20 (100)</td>
<td>0.562</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
<td>6 (100)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>dofetilide</td>
<td>35 (77.8)</td>
<td>10 (22.2)</td>
<td>45 (100)</td>
<td>0.652</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>3 (75.0)</td>
<td>1 (25.0)</td>
<td>4 (100)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>dofetilide</td>
<td>53 (81.6)</td>
<td>12 (18.5)</td>
<td>65 (100)</td>
<td>0.598</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>8 (80.0)</td>
<td>2 (20.0)</td>
<td>10 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Note. AF=atrial fibrillation. NSR=normal sinus rhythm. Sig*=Fishers Exact

1. **Research Questions 1 and 2**— Association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide between males and females at the 1-month, 3-month, and 6-month post-loading interval.

Pearson’s chi-square test was performed on the entirety of the data to determine if there was a significant association between the dependent and independent variables. A total of 79 ECGs were obtained one-month post-drug loading. At the one-month post-drug loading period, 5 (100%) females with paroxysmal AF had converted to NSR compared to 15 (93.8%) males with paroxysmal AF; and 16 (72.7%) females with persistent AF had converted to NSR compared to 30 (83.3%) males with persistent AF. The test assumption for Pearson’s chi-square and cross-tabulation analysis requires expected cell counts to be above 5. This analysis found that 6 cells had an expected value less than 5, therefore Fisher’s Exact test was used to evaluate statistical significance. Based on Fisher’s Exact test, there was no significant association between gender and conversion and sustainment of NSR from
paroxysmal or persistent AF at the one-month post-drug loading period, $p = .167$. See Table 4-4.

A total of 76 ECGs were obtained three-months post-drug loading. At the three-month post-drug loading period, 5 (100%) females with paroxysmal AF had converted to NSR compared to 15 (100%) males with paroxysmal AF; and 18 (81.8%) females with persistent AF had converted to NSR compared to 27 (79.4%) males with persistent AF. The test assumption for Pearson’s chi-square and cross-tabulation analysis were violated rendering the need for Fisher’s exact test which found no significant association between gender and conversion and sustainment of NSR from paroxysmal or persistent AF at the three-month post-drug loading period, $p = .057$. See Table 4-5.

A total of 75 ECGs were obtained six-months post-drug loading. At the six-month post-drug loading period, 4 (100%) females with paroxysmal AF had converted to NSR compared to 10 (71.4%) males with paroxysmal AF; and 19 (84.4%) females with persistent AF had converted to NSR compared to 28 (80.0%) males with persistent AF. The test assumption for Pearson’s chi-square and cross-tabulation analysis were violated with a total of 5 cells having expected cell counts less than 5, therefore Fisher’s exact test was evaluated to determine statistical significance. Fisher’s exact test found no significant association between gender and conversion and sustainment of NSR from paroxysmal or persistent AF at the six-month post-drug loading period, $p = .446$. See Table 4-6.

Pearson’s chi-square test and cross-tabulation were used to evaluate an association between gender and the use of sotalol or dofetilide and the conversion and sustainment of NSR from
paroxysmal or persistent AF at the 1-month, 3-month, and 6-month post-drug loading intervals. At the 1-month post-drug loading interval 79 ECGs were evaluated. Twenty-seven of the patients were female and 52 of the patients were male. Of the 27 female patients, 21 were on dofetilide and 6 were on sotalol. Of the 52 male patients, 47 were on dofetilide and 5 were on sotalol. At the 1-month post-drug load interval, 18 (85.5%) of females on dofetilide had converted to NSR compared to 42 (89.4%) of males on dofetilide; and 3 (50%) of females on sotalol had converted to NSR compared to 3 (60%) of males on sotalol. Test assumption for Pearson’s chi-square test had been violated, therefore Fisher’s exact test found a statistically significant association between gender and the use of sotalol or dofetilide in the conversion and sustainment of NSR from paroxysmal or persistent AF, \( p = 0.015 \). Expected and observed counts in this evaluation were nearly equal. The significance of this value will benefit from future research on a larger and more gender diverse sample size to clearly understand this particular outcome. See Table 4-7. 

At the 3-month post-drug loading interval 76 ECGs were evaluated. Twenty-seven patients were female, and 49 patients were male. Of the 27 female patients, 21 were on dofetilide and 6 were on sotalol. Of the 49 male patients, 45 were on dofetilide and 4 were on sotalol. At the 3-month post-drug load interval, 18 (85.7%) of females on dofetilide had converted to NSR compared to 39 (8.7%) of males on dofetilide; and 5 (83.3%) of females on sotalol had converted to NSR compared to 3 (75%) of male on sotalol. Test assumption for Pearson’s chi-square test had been violated, therefore Fisher’s exact test found no significant association between gender
and the use of sotalol or dofetilide in the conversion and sustainment of NSR from paroxysmal or persistent AF, $p=.444$. See Table 4-8.

At the 6-month post drug loading interval 75 ECGs were evaluated. Twenty-six patients were female, and 49 patients were male. Of the 26 female patients, 20 were on dofetilide and 6 were on sotalol. Of the male patients, 45 were on dofetilide and 4 were on sotalol. At the 6-month post-drug load interval, 18 (90%) of the females on dofetilide had converted to NSR compared to 35 (77.8%) of males on dofetilide; and 5 (83.3%) of females on sotalol had converted to NSR compared to 3 (75%) of males on sotalol. Test assumption for Pearson’s chi-square test had been violated, therefore Fisher’s exact test found no significant association between gender and the use of sotalol or dofetilide in the conversion and sustainment of NSR from paroxysmal or persistent AF at the 6-month drug-loading interval, $p=.598$. See Table 4-9.

2. **Research Questions 3 and 4**—Association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide between non-whites and whites at the 1-month, 3-month, and 6-month post-loading interval.

Evaluating the association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide between non-whites and whites at the 1-month, 3-month, and 6-month post-drug loading interval was not able to be assessed due to the lack of non-white subjects in the study. This question may be addressed with a more racially diverse larger sample size.
4.4.1 **Hypothesis**

The null hypothesis is as follows: There is no association between males and females or whites and non-whites in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide. No statistical significance was found in the conversion and sustainment of NSR in either of these groups, therefore the null hypothesis is accepted in this sample.

**4.5 Conclusion**

In conclusion, this chapter has analyzed demographic data from the catchment area of the study as well as the study subjects. Data were compared between females and males and whites and non-whites and the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide at the 1-month, 3-month, and 6-month post drug-loading intervals. Chapter V will provide a discussion of the findings, limitations, and future research needed in this area.
CHAPTER V

CONCLUSIONS, DISCUSSION, AND RECOMMENDATIONS FOR FUTURE RESEARCH

5.1 Introduction

The following chapter concludes this report. A review of the research problem and purpose of the study will be presented followed by a discussion and interpretation of the findings based on the research questions. The chapter will conclude with a description of limitations and recommendations for future research.

5.2 Statement of the Problem

Based on the literature, it has been shown that the safety, efficacy, and side effects of drugs vary based on gender, racial, ancestral, and ethnic lines (Knepper & McLeod, 2018). In the clinical trials performed to develop and market new drugs, females and non-whites are largely underrepresented rendering the safety and efficacy data obtained for these groups insufficient (King, 2002). As a result of the data being derived from predominantly white male cohorts, these data may then be inappropriately extrapolated for clinical use in females and non-whites resulting in consequential adverse outcomes ranging from mild to severe side-effects to death (Ramamoorthy, et al., 2013). Post-market studies and reporting from FAERS may subsequently reveal patterns of adverse outcomes potentially leading to FDA regulation of drugs that may include labeling restrictions, post-market population specific prescribing, black-box
warnings, and in some cases, revocation of FDA approval (Ramamoorthy et al., 2013; Weyant, 2017).

### 5.3 Purpose of the Study

The purpose of this study was to identify any association between females and males, and whites and non-whites diagnosed with paroxysmal or persistent AF in the conversion and sustainment of NSR using sotalol or dofetilide. This chapter contains discussion and future research possibilities to help answer the research questions:

(R1): Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol between males and females at the 1-month, 3-month, and 6-month post-loading interval?

(R2): Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using dofetilide between males and females at the 1-month, 3-month, and 6-month post-loading interval?

(R3): Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol between whites and non-whites at the 1-month, 3-month, and 6-month post-loading interval?

(R4): Is there an association in the conversion and sustainment of NSR from paroxysmal or persistent AF using dofetilide between whites and non-whites at the 1-month, 3-month, and 6-month post-loading interval?

The overarching hypothesis of this study was that there was no association between males and females or whites and non-whites in the conversion and sustainment of NSR from
paroxysmal or persistent AF using sotalol or dofetilide. The findings of this study support the hypothesis.

5.4 Interpretation of Findings

Diversity in the participation of clinical trials is paramount in obtaining data that is accurate to determine the efficacy and safety of drugs. Factors impacting the outcome of this study as it relates to the effectiveness of sotalol and dofetilide may be because this cohort was lacking in diversity related to gender and race. The catchment area for the location of this study was urban and rural. The population consisted of 84.6% whites, 3.6% blacks, 8% Hispanics, 1% Native American Indian/Alaskan, and 1% Asian.

5.4.1 Association in the conversion and sustainment of NSR using sotalol or dofetilide between males and females

This study found that there was an association between males and females in the conversion and sustainment of NSR from paroxysmal or persistent AF using sotalol or dofetilide at the 1-month post-drug loading interval, \( p = .015 \). Upon further evaluation of the Pearson’s chi-square and Fisher’s Exact tests of observed versus expected values, more subjects were expected to convert to NSR using sotalol; 9.2 expected compared 1.8 observed. This could be the cause of the statistically significant Fisher’s Exact test, however in order to obtain full clarity regarding the significance of this result, it may be necessary to run this study on a larger and more gender diverse sample size. Statistical significance at this stage would not necessarily affect clinical use of these drugs. With respect to the association between males and females in the sustainment
and conversion of NSR from paroxysmal or persistent AF using sotalol or dofetilide at the 3-month and 6-month post drug-loading intervals, there was no association found, $p=.444$ and $p=.598$ respectively. The gender demographics of this study are in line with clinical trials of sotalol and dofetilide by the FDA in 2018. In this study, 65% of subjects were male and 35% were female. In the clinical trial performed by the FDA in 2018 for sotalol, 64% of study participants were male and 36% were female, while in the clinical trial for dofetilide 70% were male and 30% were female.

5.4.2 Association in the conversion and sustainment of NSR using sotalol or dofetilide between whites and non-whites

Race could not be accurately evaluated in this study due to the low number of non-white participants. Of the study subjects, 80 were white and 4 were non-white. Pearson’s chi-square analysis requires that there be at least 5 subjects in each category, however race did not meet that requirement and thus was not analyzed. This finding is consistent with historical patterns that show non-whites, especially blacks, are far less likely to participate in clinical trials with African and African-American participation ranging between 1.8% and 3.5% (Knepper & McLeod, 2018).

5.4.2.1 Contributing Factors to Reduced Enrollment of Females in Clinical Trials

Many factors may impact the representation of women in clinical trials. Differential enrollment in clinical trials based on gender has been historically documented in the literature.
According to Ramasubbu et al. (2001) clinical trials in oncology enrolled on average 34% women, infectious disease enrolled 39% women, cardiology enrolled 25% women, and gastroenterology enrolled 37% women. Growth in the strength of evidence-based medicine and the knowledge of gender-specific pharmacokinetics and pharmacodynamics raise the importance of females being included in clinical trials. The literature points to many reasons why females are less likely to participate or be enrolled in clinical trials. According to Ramasubbu et al. (2001), designers of clinical research may exclude females in order to obtain a more homogenous sample of participants with similar characteristics in an effort to improve the power of their study, reduce variation, and in turn require a smaller sample size and reduced budgets. Also, fear of legal liability as it pertains to teratogenicity, child-bearing ability, and pregnancy may deter researchers from increasing the enrollment of female subjects in clinical drug trials (Bush, 1994; Ramasubbu et al., 2001). Socioeconomic status, household responsibilities such as childcare and work, lack of financial independence, lack of transportation, and health insurance are also key reasons why females may choose not to participate in clinical trials (Bush, 1994; Ramasubbu et al., 2001). Across all racial and ethnic lines in the U.S., women are paid 82 cents for every dollar paid to men (National Partnership for Women and Families [NPWF], 2020). According to the NPWF (2020) the median income for a woman with a full-time, year-round job is $45,094 compared to $55,291 for a man with a full-time, year-round job; a difference of $10,194 per year. Women of color in particular experience a much sharper gender wage gap than their white counterparts. Latina are paid 54 cents for every dollar paid to a white, non-Hispanic man, while black women are paid 62 cents, and Native American women are paid 57
cents. The median annual income for a Latina in the U.S. who holds a full-time, year-round job is $33,450, a black woman is $38,036, and a Native American women $34,466 while the median annual income for a white, non-Hispanic man who holds a full-time year-round job is $61,576. Filling the wage gap held between women, and especially women of color, compared to white men in the U.S. could translate into more money for education, childcare, and employer-based health insurance. Relief of these financial burdens and the ability to afford health care, transportation, and childcare coverage could contribute to a desire for women and women of color to participate in clinical trials.

5.5 Contributing Factors to Reduced Enrollment of Non-whites in Clinical Trials

It has long been known that African-Americans harbor deep mistrust for the health care system compared to whites (Boulware, Cooper, Ratner, LaVeist, & Powe, 2003; LaVeist, Nickerson, & Bowie, 2003). This mistrust has been linked to underutilization of health care service, concern of unwitting enrollment in potentially harmful medical experiments, a consequence of historical segregation in hospitals, and discourteous and maltreatment by hospital personnel and health care professionals (Brandon, Isaac, & LaVeist, 2005). The legacy of the Tuskegee Study of Untreated Syphilis in the Negro Male (The Tuskegee Study) lives on. The Tuskegee Study was a 40 year-long study conducted by the U.S. Public Health Service that involved the intentional deception and infection of African-American males with syphilis and the denial of proven successful treatment. The purpose of the study was to track and document the natural course of the disease from infection to death of the host (Brandon et al., 2005). This is
one of the most common cited reasons for mistrust in the health care system by African-Americans (Brandon et. al, 2005). Other barriers experienced by blacks related to entry into clinical trials include economic disadvantages, lack of awareness of study programs, and communication barriers. A study performed by Gorelick et al. (1998) attempted to determine reasons why African-Americans 1) enrolled and remained, 2) withdrew, or 3) refused to participate in the African-American Antiplatelet Stroke Prevention Study (AAASPS). This was a small study performed at Rush Medical Center in Chicago with a total $n=29$. Participants of the study were separated into three groups. Group 1 (patients who remained in the study, $n=19$); group 2 (patients who withdrew from the study, $n=4$); and group 3 (patients who refused to participate in the study, $n=6$). Five content area questions were posed to the participants:

1. What were your reasons for participating (voluntarily withdrawing, refusing to participate) in the AAASPS?
2. What circumstances or events may have influenced your decision to participate (withdraw, refuse to participate) in the AAASPS?
3. Was the information regarding the study explained to you in words or terms that you could easily understand?
4. Did the study coordinator treat you in a respectful manner?
5. What was the opinion of your family members or friends regarding your being asked to participate in the AAASPS?

The results of the study are as follows;
Group 1: Patients who remained in the study

Of the 19 participants who remained in the study, 16 reported that they participated to reduce the risk of another stroke and 6 reported their desire to find a cure for stroke or to help others.

Group 2: Patients who withdrew from the study

Of the 4 patients who withdrew from the study, all patients cited concerns of being subject to experimentation and the possibility of being used as a “guinea pig.”

Group 3: Patients who refused to participate in the study

Of the 6 patients who refused to participate in the study, 2 patients cited concerns of being used as a “guinea pig” and 3 cited the desire to keep their current medications the same or being too busy to participate. The last participant declined to give reason for not participating.

5.6 Strategies for Improving Enrollment of Non-whites and Females in Clinical Trials

Recruitment and retention in studies are paramount to the success of clinical trials. Due to the deep and long history of distrust and maltreatment by the medical industry of non-whites and in particular, blacks, this is challenging. In the study by Gorelick et al. (1998) they identified a recruitment triangle that may help to predict a patient’s likelihood of participating in clinical trials. This recruitment triangle consisted of three walls; the patient, the patient’s primary care provider and other allied medical personnel, and key family and friends.
According to Gorelick et. al (1998), the walls of the recruitment triangle are held together by social support, trust in the designers of research and study personnel, and education about the nature of the research. Trust may be established by using culturally sensitive staff and improving racial and language coherence, treating patients with respect, and clearly communicating and educating the patients and key family and friends on the tenants of the research (Gorelick et al., 1998). Using a low-pressured approach may also help to quell the notion of being experimented upon by the medical community. Collapse of any of the walls of the recruitment triangle
according to Gorelick et al. (1998) may repel blacks from contributing to clinical trials. Taking into account this emergent recruitment triangle could help to break down barriers to enrollment.

The NIH Revitalization Act of 1993 directed the NIH to publish guidelines promoting the inclusion of women and minorities in major federally funded clinical research (NIH, 1994). The guidance from the NIH included guidelines for a) “the circumstances under which the inclusion of women and minorities as study subjects in projects of clinical research is appropriate, b) the manner in which clinical trials are required to be delegated and carried out, and c) the operation of outreach programs. The statute states that:

- Women are included as study subjects in each project of such research, and
- Members of minority groups are included in such research (p. 14508)”

Revitalization of the statute adds additions stating that the “NIH must:

- Ensure that women and members of minorities and their subpopulations are included in all human subjects research
- For Phase III clinical trials, ensure that women and minorities and their subpopulations must be included such that valid analysis of differences in intervention effect can be accomplished
- Not allow cost as an acceptable reason for excluding these groups and,
- Initiate programs and support for outreach efforts to recruit these groups into clinical studies (p. 14508).”

The revised guidelines also required women of childbearing ability to be included in all phases of clinic trials for drug development (NIH, 2016). The NIH has gone further amending the
guidelines in 2001 to require the reporting on gender, race and ethnicity in federally funded clinical trials (Bowleg, 2012).

Understanding and addressing concerns and questions of females and minorities with understandable and sensitive feedback in the research process is paramount if the goal is to obtain and keep them enrolled in clinical trials (Martin, Negron, Balbierz, Bickell & Howell, 2013). In order to achieve truly generalizable data from clinical trials efforts must be taken to include non-whites and minorities in clinical trials.

5.7 Limitations

The results of this study must be interpreted within the context of its limitations. This study was performed at one institution with a catchment area that was >80% white. The study subjects were predominantly white and male. This makes generalizability to non-whites and females and then extrapolation of data results to these populations unreliable. As the catchment area was predominantly white, race was not able to be included in statistical analysis leaving data for non-whites lacking in this study. With respect to race, for the study subjects, it was self-documented leaving room for error or personal preference that could not be accounted for during the research process. As mentioned previously, AF can co-occur with other dysrhythmias impacting the efficacy of medical and procedural treatment. This study did not take into account the fact that other dysrhythmias may have impacted the outcome of the patient’s ECGs. It is also noteworthy that some patients in the study may have required additional treatment to sustain NSR in addition to sotalol and dofetilide. Additional and alternative treatments may have an
impact on the efficacy of the two drugs that was not studied in this research. Comorbidities like HTN, OSA, CAD, and valvular heart disease may cause, exacerbate, or reduce the efficacy of treatment of AF (January et al., 2014). Many of the study subjects were diagnosed with one or more of these comorbidities which may have had an impact on the outcome. Behavioral characteristics also impact the outcome of treatment of AF. Medication non-compliance, cigarette smoking, excessive caffeine intake, alcohol use or use disorder, illicit drug use, having a sedentary lifestyle or excessive exercise can have an impact on treatment outcomes (January et al., 2014). Although patients are counseled to avoid these behaviors, it was not possible to insure total adherence. With respect to ECGs, it is noteworthy that during this study, they were only evaluated at the 1-month, 3-month, and 6-month post-drug loading interval. This gives a brief view of the patient’s heart rhythm while they are in a controlled environment. These ECGs do not represent the patient’s heart rhythm outside of this environment rendering complete assessment impossible. It is very likely that the patients may have had AF or other dysrhythmias that were not documented during the course of this study.

5.8 Recommendations for Future Research

This study brings to light the importance of including females and non-whites in clinical trials. In order to improve upon this research, including multiple institutions with more diverse catchment areas and a larger sample size may help to achieve generalizable results and include accurate data specifically pertaining to females and non-whites. As comorbidities do play a role in the outcome of treatment of AF, including those other medical problems as variables will
assist the clinical provider in determining the potential efficacy in treatment using sotalol or dofetilide. Along with the aforementioned comorbidities being represented in future studies, including other dysrhythmias will also provide valuable information related to how they affect the outcome of treatment of AF with sotalol or dofetilide. Lastly, AF may cause no symptoms or severely debilitate patients and negatively affect their quality of life (January et al., 2014). Future studies may be done to determine the level of improvement in a patient’s quality of life and their rate of conversion to NSR.

In summary, these findings represent implications for future research and contribute to a larger body of work highlighting the need to include females and non-whites in clinical trials. More research is needed in an effort to obtain safety and efficacy information of sotalol, dofetilide, and other approved drugs for underrepresented populations.

5.9 Conclusion

Clinical research can potentially advance the health of all individuals in society, but for that to happen, clinical trials must become more diverse. This is not only a matter of reducing health disparities based on gender, race, and ethnicity, but of positively impacting social justice and strengthening science and society (Perez-Stable, 2018). Intersectionality, as a means to shed light on the impact discriminating social identities have on health care and other areas of importance, does well to reveal the breaches in clinical research that lead to inaccurate and, at times, dangerous data for subpopulations such as females and non-whites. This theoretical framework provides science and other industries with valuable foresight and historical insight that has the potential to identify and rectify the privilege and oppression woven into American
society. This research holds true to inequities in clinical trials across the country and abroad in its representation of predominantly white males. As no statistical significance was found in the analysis of the data, the overarching historical problem remained; a lack of females and non-white participants. It is noteworthy that participation of females and non-whites does not squarely land at the feet of motivation of these two groups. What must also be considered are access to clinical trials, health insurance coverage, wage gaps, historical mistrust, education, and communication. These areas must be addressed and remedied if females and non-whites are to be better represented in clinical trials.
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APPENDICES

A. Western Michigan University Human Subjects Institutional Review Board Letter of Approval

WESTERN MICHIGAN UNIVERSITY

Date: June 8, 2020
To: Kieran Fogarty, Principal Investigator
    Nicole Bradford, Student Investigator for dissertation
From: Amy Naugle, Ph.D., Chair
Re: IRB Project Number 20-06-11

This letter will serve as confirmation that your research project titled “Cardiac Electrophysiology: Exploring Gender and Racial Outcomes of Paroxysmal and Persistent Atrial Fibrillation Using Sotalol and Dofetilide” has been approved under the exempt category of review by the Western Michigan University Institutional Review Board (IRB). The conditions and duration of this approval are specified in the policies of Western Michigan University. You may now begin to implement the research as described in the application.

Please note: This research may only be conducted exactly in the form it was approved. You must seek specific board approval for any changes to this project (e.g., add an investigator, increase number of subjects beyond the number stated in your application, etc.). Failure to obtain approval for changes will result in a protocol deviation.

In addition, if there are any unanticipated adverse reactions or unanticipated events associated with the conduct of this research, you should immediately suspend the project and contact the Chair of the IRB for consultation.

The Board wishes you success in the pursuit of your research goals.

A status report is required on or prior to (no more than 30 days) June 7, 2021 and each year thereafter until closing of the study. The IRB will send a request.

When this study closes, submit the required Final Report found at https://wmich.edu/research/forms.

Note: All research data must be kept in a secure location on the WMU campus for at least three (3) years after the study closes.
B. Mercy Health Human Subjects Institutional Review Board Letter of Approval

NOTICE OF IRB EXEMPT APPROVAL

To: Nicole Love PAC, MSM
    1355 Dudley Ave.
    Muskegon, MI 49442

Re: IRB# 20-0528-4
    Cardiac Electrophysiology: Exploring Gender and Racial Outcomes of Paroxysmal and Persistent Atrial Fibrillation Using Sotalol and Dofetilide

Date: 06/01/2020

This is to inform you that Mercy Health Regional Institutional Review Board (IRB) has reviewed your proposed research project and has determined that it meets the criteria for an exempt study, under exempt category 4 (iii). This determination was made based on the exempt criteria put forth by the federal regulations as defined in 45 CFR 46.101(b). Our review and approval includes the following:

- Waiver of HIPAA Authorization
- Protocol, Version 05/28/2020
- Data Collection Sheet, Version 05/05/2020

As this study has received an exempt determination, submission of continuing review reports to the IRB will not be required. However, we request you advise the IRB when you have completed your project, so we may mark our file accordingly.

The IRB does require notification of any changes in the protocol or procedures. If this occurs, please submit an Amendment form in IRBManager.

If you have any questions, please contact our office at the number listed below.

G. Robert DeYoung, PharmD, FCCP, BCPS
IRB Chairperson

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